RECOVERY FROM DEPRESSIVE ILLNESS AFTER ELECTROCONVULSIVE THERAPY

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The true science and study of man is man

Pierre Charron

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DECLARATION

Apart from the acknowledgements made overleaf, I declare that the work described, and this thesis, are entirely my own work.

Signed
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ABSTRACT

Experiment One Plasma concentrations of oxytocin-associated neurophysin and prolactin were measured before and after the first treatment in a course of electro-convulsive therapy (ECT) given to 25 depressed patients. Plasma neurophysin concentration was measured by the radioimmunoassay (RIA) of Robinson (1975). The percentage peak increase in plasma neurophysin concentration was three times greater ($p < 0.001$) in the 16 depressed patients who had a good outcome two months after the last ECT compared with the nine who did not. The rise in plasma neurophysin concentration correlated ($\rho = 0.46$, $p < 0.05$) with improvement in symptoms measured by the Hamilton Rating Scale for Depression (HRSD). There was no difference in the percentage peak increase in plasma prolactin concentration between patients who had a good outcome two months after the last ECT and those who did not. The rise in plasma prolactin concentration did not correlate with improvement in HRSD score.

Experiment Two Serum concentrations of the vasopressin- ($hNpI$) and oxytocin-associated neurophysins ($hNpII$) were measured by the RIA of Legros et al. (1969) before and after the first ECT in a course of treatment given to 19 unipolar depressed patients. The percentage peak increase in $hNpII$ was four times greater ($p < 0.001$) in the six patients who had a good outcome two months after the last ECT than in the patients who had a poor outcome. The rise in serum $hNpII$ correlated with improvement in HRSD score ($r = 0.50$, $p < 0.05$) and improvement in score on the Montgomery and Asberg Depression Rating Scale ($r = 0.47$, $p < 0.05$). The rise in serum $hNpI$ concentration did not correlate with improvement. There were no significant correlations between
spike-wave activity or total seizure activity measured by a six-channel electroencephalogram (EEG) and the rise in either of the neurophysins.

**Experiment Three** Serum concentrations of hNpI and hNpII were measured at the first and last treatments in a course of ECT given to 17 unipolar depressed patients (seven of whom also took part in Experiment Two). There were no significant differences in the average release of either neurophysin between the first and last treatments. There were no significant correlations between alterations in the release of the neurophysins between the first and last treatments and improvement in symptoms of depression.

Conclusions Although there is a correlation between the release of hNpII after the first ECT and improvement in symptoms of depressive illness, the correlation is not sufficiently close to be of clinical utility in the prediction of ECT outcome. The reason for the correlation is not known. There was no support for the hypothesis that the release of hNpII was a correlate of cerebral seizure activity. The release of hNpII may be a sensitive measure of electrical stimulation in the midbrain or may occur at the same time as the release of a neurotransmitter with mood-regulating activity.
<table>
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<td>Adrenocorticotropic</td>
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<td>BDI</td>
<td>Beck Depression Inventory</td>
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<td>Bmax</td>
<td>Maximum binding</td>
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<td>BPRS</td>
<td>Brief Psychiatric Rating Scale</td>
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<tr>
<td>Ca-ATPase</td>
<td>Calcium-dependent adenosinetriphosphatase</td>
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<tr>
<td>CNS</td>
<td>Central nervous system</td>
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<td>CRF</td>
<td>Corticotropin releasing factor</td>
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<td>CSF</td>
<td>Cerebrospinal fluid</td>
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<td>DST</td>
<td>Dexamethasone suppression test</td>
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<td>EEG</td>
<td>Electroencephalogram</td>
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<td>ECS</td>
<td>Electroconvulsive shock</td>
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<td>ECT</td>
<td>Electroconvulsive treatment</td>
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<td>ESN</td>
<td>Oestrogen-stimulated neurophysin</td>
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<td>GH</td>
<td>Growth hormone</td>
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<tr>
<td>hNpI</td>
<td>Vasopressin-associated neurophysin</td>
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<tr>
<td>hNpII</td>
<td>Oxytocin-associated neurophysin</td>
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<tr>
<td>HPA</td>
<td>Hypothalamic-pituitary-adrenocortical</td>
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<td>HRSD</td>
<td>Hamilton Rating Scale for Depression</td>
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<td>5-HT</td>
<td>5-hydroxytryptamine</td>
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<td>MADRS</td>
<td>Montgomery and Asberg Depression Rating Scale</td>
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<td>MAO</td>
<td>Monoamine oxidase</td>
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<td>MHPG</td>
<td>3-methoxy-4-hydroxyphenylglycol</td>
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<td>MRC</td>
<td>Medical Research Council</td>
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<td>NIADDK</td>
<td>National Institute of Arthritis Diabetes and Diseases of the Kidney</td>
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<tr>
<td>NIMH</td>
<td>National Institute of Mental Health</td>
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<tr>
<td>NS</td>
<td>Not statistically significant</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>NSN</td>
<td>Nicotine-stimulated neurophysin</td>
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<td>REM</td>
<td>Rapid eye movement</td>
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<tr>
<td>RIA</td>
<td>Radioimmunoassay</td>
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<td>SD</td>
<td>Standard deviation</td>
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<td>SEM</td>
<td>Standard error of the mean</td>
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<td>SPECT</td>
<td>Single photon emission computed tomography</td>
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<td>TRH</td>
<td>Thyrotrophin releasing hormone</td>
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<td>TSH</td>
<td>Thyroid stimulating hormone</td>
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Depressive illness is the commonest psychiatric illness. In most episodes of illness the sufferer never receives any medical or psychiatric help (Holden, 1986). When an episode of illness is treated by a psychiatrist, electroconvulsive therapy (ECT) is necessary in only a minority of cases. The Royal College of Psychiatrists has recommended ECT in the treatment of depressive illness which is "severe, long-lasting or life-threatening" or where there are reasons for seeking rapid improvement in certain symptoms, for example, suicidal inclination. ECT may also be used where physical illness contraindicates the use of antidepressant drug treatment (ECT Sub-Committee of the Research Committee of the Royal College of Psychiatrists, 1989). Although used to treat a minority of episodes of depressive illness, depressive illness is so common that in 1988 nearly 200 depressed patients were treated by ECT in the Royal Edinburgh Hospital, which serves a population of approximately 440,000 people. An average course of ECT consists of seven treatments spaced over two or three weeks. The majority of contemporary depressed patients treated by ECT improve, but about 15% gain little or no benefit from a course of treatment (Rich et al., 1984).

The major aim of the work in this thesis was to study the relationship between the increased release of pituitary peptides that occurs in the minutes after ECT and the extent of improvement in symptoms of depressive illness after a course of ECT. In the first experiment, the peptides under study were prolactin and oxytocin-associated...
neurophysin, but later experiments concentrated on the relationship of oxytocin-associated neurophysin release after the first ECT to recovery from depressive illness.

A proven relationship would provide an important clue about the mode of action of ECT and, if sufficiently strong, the relationship may be of clinical value in the identification of depressed patients who will go on to recover after a course of ECT. Conversely, the relationship may be of value in identifying those patients who would otherwise receive a course of ECT without benefit.

The second aim of the work was to develop a reliable method of measuring cerebral seizure activity with simultaneous recording by electroencephalogram during ECT. This procedure was necessary to understand more fully the relationship between the release of oxytocin-associated neurophysin and recovery.

The work of this thesis was conducted between 1985 and 1989 while I was a Lecturer in the Department of Psychiatry of the University of Edinburgh. The staff and facilities of the Department provide important support for psychiatrists who are interested in research and the presence of the MRC Brain Metabolism Unit is an asset. Perhaps the most important attribute of the Department is the close link that exists with the Royal Edinburgh Hospital. Without the support and co-operation of the patients, doctors and nurses of the Hospital, the work of this thesis would not have been possible.
CHAPTER TWO

REVIEW OF THE LITERATURE

Introduction

The major aim of the work in this thesis is to study the relationship between the effects of electroconvulsive therapy (ECT) on pituitary hormone release and the extent of improvement in symptoms of depressive illness over a course of treatment. A close correlation between a biological effect of ECT and the extent of improvement may be of value in the identification of depressed patients who will recover after a course of ECT. The review of the literature consists of the definition of important terms, an explanation for the contemporary interest in the biological effects of ECT, a discussion of the methodological difficulties of much of this work, and, finally, a review of the biological measures which have been studied. A major part of the review is devoted to the effects of ECT on the release of pituitary hormones.

Definition of terms

Depressive illness The word 'depression' is used in several ways by the layman and the psychiatrist. It may refer to a temporary mood, a symptom, a syndrome, and sometimes a psychiatric illness (Canoro, 1985). The characteristic clinical feature of depressive illness is a disturbance of mood which is prominent, persistent and usually associated with other symptoms. The disturbance of mood is usually, but not always,
experienced as a sadness. This is associated with the reduced capacity to experience pleasure, reduced interest in the environment, and reduced energy (Cancro, 1985). Associated symptoms include diurnal variation in mood, loss of appetite, weight loss, and sleep disturbance. Psychological disturbances include inappropriate guilt, impaired concentration and poor short-term memory. These associated symptoms are sometimes referred to as 'biological' (Hamilton, 1986), 'vegetative' (Fink, 1979) or 'endogenous'. The term endogenous refers to a debate (not yet resolved) that constitutional factors are more important than environmental factors in the aetiology of such illnesses (Kendell, 1976). In severe depressive illness, marked psychomotor retardation may lead to stupor and a failure to eat or drink sufficiently, and the marked disturbance of thinking can lead to delusions of guilt or nihilism. Suicide is not uncommon; about 15% of patients who suffer recurrent mood disorder may go on to kill themselves (Kendell, 1988).

If the patient has ever suffered from mania, the mood disorder is classified as a bipolar disorder; otherwise the mood disorder is classified as a unipolar disorder (Cancro, 1985).

Electroconvulsive therapy (ECT) is the application of an electric current to the head with the aim of inducing a controlled tonic clonic or grand mal seizure, usually at intervals of days, to achieve an improvement in an abnormal mental state (Fink, 1979). When ECT was first used in 1938 and for some years thereafter, it was given without an anaesthetic, so-called unmodified ECT. The introduction of short-acting anaesthetic agents and muscle relaxant drugs led to the introduction of modified ECT when the electrical stimulus is applied to an unconscious
and partially paralysed patient. Most depressed patients require a course of ECT which usually consists of between four and eight treatments (ECT Sub-Committee of the Research Committee of the Royal College of Psychiatrists, 1989). The first ECT machines were little more than transformers which applied a sine-wave stimulus of 110 volts applied from electrodes placed on each side of the head (bilateral electrode placement). Contemporary ECT machines are much more sophisticated and discharge a fixed amount of current in a series of brief pulses. Brief-pulse stimuli can induce seizures with less current than sine-wave stimuli (Fink, 1979). Certain of the cognitive side-effects of ECT are lessened by the use of unilateral electrode placement where current is passed through the non-dominant cerebral hemisphere by electrodes placed on the temple and occipital or parietal areas (Fink, 1979).

ECT is to be contrasted with electroconvulsive shock (ECS) which is an experimental laboratory model of ECT in which electric shocks are given singly or repeatedly at daily intervals to laboratory animals, usually rodents and occasionally primates. ECS may be unmodified or given after an anaesthetic. Much of the biochemistry of repeated seizures has been studied in such animal models (Green & Nutt, 1987).

Terminology of seizures There is considerable debate about the terminology of the clinical and electroencephalographic features of seizures (Binnie, 1988). The term 'seizure', which is approved by the International League against Epilepsy (1981), means a sudden fit or apoplexy which is defined as a sudden malady which arrests the power of sense and motion (Oxford English Dictionary, 1979); thus, the term seizure does not distinguish between cerebral and motor function. In
this review, the term 'convulsion' will be used to describe the involuntary contraction or drawing up of the limbs or spasms of the muscles (Oxford English Dictionary, 1979) that may occur during a seizure. The aim of ECT is to induce a generalized tonic clonic seizure in which the convulsive activity first involves a tonic contraction of muscles and then gives way to clonic convulsive movements which are bilateral (International League against Epilepsy, 1981). The use of short-acting muscle relaxant drugs in modern ECT practice modifies the appearance of convulsive activity. Intra-cranial electrodes applied to the cortex show that tonic clonic seizures are associated with a spike-wave electrical discharge (Binnie, 1988). A spike wave on a recording by electroencephalogram (EEG) is a transient wave, clearly distinguished from background activity, with a pointed peak and a duration under 70 ms (Binnie, 1987) or 80 ms (Binnie, 1988). The use of scalp electrodes in EEG recording during a tonic clonic seizure results in a loss of amplitude in the spike waves and a proportion of spike waves will not be seen, dependent on the area of the cortex involved in the seizure (Goldensohn, 1979; Binnie, 1988). The spike wave has been called the 'signature of a seizure' (Martin, 1985) and it is the presence of bilateral spike-wave activity which characterizes generalized tonic clonic seizures and distinguishes these from focal seizures (Martin, 1985; Binnie, 1988). The phases of cerebral seizure activity which occur during ECT have been described in detail (Small et al., 1973; Weiner, 1982; Brumback & Staton, 1982). EEG recording with surface electrodes during ECT has shown that immediately after the electrical stimulus there is a brief phase of high frequency beta activity (in excess of 14 Hz) followed by a phase of high frequency spike-wave activity which gradually becomes more rhythmic at 2.5 - 4 Hz and gradually the
spike waves are interspersed by a larger, less frequent wave (spike and wave activity) until the frequency and amplitude of all waves gradually subside. The EEG record of the seizure may end abruptly ('the fit switch'). Immediately after these phases of cerebral seizure activity, there is always at least partial suppression of the amplitude and frequency on the EEG recording and often the record is almost isoelectric immediately after.

Recovery from depressive illness implies a 'return to health' (Oxford English Dictionary, 1979), a state which will be sought after by both the psychiatrist and the patient. One of the major methodological problems in the study of ECT is that there is no generally agreed definition for recovery, the goal of a successful course of ECT. This matter will be discussed again below.

Prediction is the ability to foretell or prophesy (Oxford English Dictionary, 1979). In medicine, the term 'prediction' is most commonly used in epidemiology where the future incidence of a disease is estimated on the presence or absence of defined risk factors or the results of a test (Fletcher et al., 1982). The overall value of a test may be summarised by its predictive accuracy, which is the proportion of all test results, both positive and negative, which correctly predict the future presence or absence of a disease. In the assessment of the accuracy of a test designed to predict treatment response, the event under study is not the development of a disease but recovery from the disease.

A hormone is a substance formed in one organ and carried by the bloodstream to another organ which it stimulates (Oxford English
The pituitary gland is an important site for the production and release of hormones, but not all substances released by the pituitary have any stimulatory effects on other organs, for example, the neurophysins. Such substances will be referred to by their chemical name only.

Contemporary ECT practice

Reviewers agree that the greater the number of the typical symptoms of depressive illness present, the greater the likelihood of recovery after ECT (Fink, 1979; Kendell, 1981; Hamilton, 1986). The well-known Medical Research Council (MRC) investigation of treatments for depressive illness showed that 84% of patients improved with ECT (MRC, 1965). Based on this and similar evidence, Fink (1979) has stated that ECT is of 'unequalled efficacy', and Hamilton (1986) believed that ECT was "one of the most effective treatments in the whole of medicine". Recent studies (using reliable operational definitions of illness) have shown that 15% of patients with typical symptoms of depressive illness do not improve (Rich et al., 1984) and that 24% of such patients do not fully recover (Andrade et al., 1988) - despite an average of about seven treatments. The accuracy of the presence of the typical features of depressive illness in the prediction of recovery in the week after a course of treatment was estimated to be 62% (Katona & Aldridge, 1984) and 72% (Andrade et al., 1988).
Interest in biological measures as predictors

There have been many attempts to identify biological measures or tests which may improve the selection of depressed patients to receive ECT. There are several reasons for this interest. First, there has never been agreement about the clinical boundaries of depressive illness (Kendell, 1976). Secondly, Abrams (1982) has argued that there is now so little clinical variability amongst depressed patients who receive ECT that the prediction of outcome based on clinical features alone may not be feasible. The third reason has been the failure of existing predictive scales to predict accurately the likelihood of recovery after ECT. These predictive scales (reviewed by Fink, 1979) make use of demographic and illness features, past psychiatric history and/or personality characteristics to calculate a final score which purported to predict the likelihood of recovery after ECT. These scales do not accurately predict improvement (Crow et al., 1984) nor recovery (Andrade et al., 1988). A recent exception was the study of Katona & Aldridge (1984) which found a predictive accuracy of 85% for the Newcastle ECT Predictor Scale (Carney et al., 1965). In part this may be because these scales were designed to predict outcome some months after ECT, but Hamilton (1986) supported Abrams in his view that the major reason for the lack of success of these predictive scales was in the contemporary selection of patients to receive ECT. He argued that these predictive scales were developed at a time when ECT was used to treat a range of illnesses with varying degrees of success for each illness. Now that ECT is restricted largely to the treatment of depressive illness which leads to a high success rate, predictive scales fail to improve on selection based on the presence of typical symptoms of depressive illness. Fourthly, the
detection and measurement of biological predictors of recovery after ECT would provide important clues about the mode of action of ECT. The fifth contemporary hope is that the identification of the characteristics of depressed patients who respond rapidly to ECT may form the basis of a subclassification of depressive illness (Fink, 1979).

Potential value of biological predictors

A patient usually consults a doctor seeking an explanation of his or her symptoms, an alleviation of suffering and help to return to normality. The selection of a treatment appropriate to a particular patient and the prediction of the likely outcome is a continual concern for doctors. Biological measures or tests may improve the clinical practice of ECT in several ways (Albala et al., 1984). Depressed patients may be identified for whom ECT would be an effective treatment. Secondly, it may be possible to monitor the process of recovery and determine the optimal end-point for a course of ECT, or thirdly, to detect patients who have successfully completed a course of ECT but are at high risk of relapse and in need of continuing supervision or vigorous continuation therapy. This review of the literature is concerned chiefly with attempts to identify depressed patients for whom ECT would be an effective treatment.

The degree of improvement after the first few treatments in a course of ECT is closely correlated with the likelihood of recovery (Price et al., 1978; Zorumski et al., 1986). There is 'no clear guidance' about how many treatments should be given when little or no clinical response is seen after the first few treatments (ECT Sub-Committee of the Research Committee of the Royal College of Psychiatrists, 1983). In such cases it
may be justified to give up to 12 treatments before the course of ECT is abandoned as being unsuccessful. The potential value of a putative biological predictor of recovery would be greatest if the biological measure or test can be made before ECT or at the first treatment. If patients who are not going to recover can be identified before or at the outset of treatment, then the likelihood of prolonged ineffective courses of ECT will be less.

Assessment of biological measures as potential predictors of recovery

Measurement is defined as the ascertainment of the spatial magnitude or quantity of something by comparison with some fixed unit (Oxford English Dictionary, 1979). Most of the biological measurements used in ECT research concern the functional organisation of the living brain and nervous system in health and disease (Weller, 1983). When measurement is made of the normal activity of a vital function, this may be referred to as a physiological measure (Oxford English Dictionary, 1979). The selection of the biological measure will depend on the formulation of the original research question or hypothesis (Bausell, 1986) and thus the prediction of ECT outcome is usually attempted on a reasoned basis or theory. In the consideration of any measurement, the most crucial question is whether the measure is appropriate to the hypothesis being tested. Once selected, the measurement procedure is usually evaluated with respect to its reliability, that is, are the numbers assigned in a stable, consistent and/or precise manner, and validity, that is, do the assigned numbers actually measure the desired attribute? (Bausell, 1986). There are considerable philosophical and practical difficulties in the assessment of the validity of a physical measure and it may be
more straightforward to ask whether a particular measurement is appropriate or useful for a specific purpose (Bausell, 1986). Certainly a measure will not be useful if it does not measure something reliably. The clinical utility of a potential biological predictor of recovery can be assessed by its predictive accuracy.

**Biological measures made before ECT**

Early studies concentrated on biological measures made before patients received any ECT (Table I), for example, the resting EEG, or the concentration of a substance in blood. A later strategy was to study the effects of administered drugs. Autonomic reactivity was assessed in Funkenstein's test which studied the effects of administered adrenaline and methacholine on blood pressure, and the sedation threshold test measured the effects of sodium amytil on the EEG. Recent studies have used administered drugs or hormones in neuroendocrine challenge tests.

**Biological measures of the consequences of ECT**

Although depressed patients who are treated by ECT are highly selected and share many clinical features, they show a variety of behavioural and physiological responses to ECT (Fink, 1979). The search for predictors of outcome may be more rewarding if based on the initial reaction to ECT itself. The use of ECT itself as a probe (Siever & Davis, 1985) or challenge (Stokes & Sikes, 1988) may reveal more about the integrity of biological control mechanisms than resting or basal measures made before ECT.
Generalized seizures lead to profound metabolic changes in the brain and systemic changes (see Meldrum, 1988, for review). Changes in cerebral metabolism which occur in the 30 minutes after a generalized seizure include raised cerebral venous pressure and increased cerebral blood flow. Systemic changes arise in two ways. First, there are physiological and metabolic changes secondary to the motor component of a seizure, for example, change in blood gases and pH, and a rise in body temperature. The dependence on the convulsive activity can be
demonstrated in experiments employing peripheral muscular paralysis. Secondly, there are autonomic changes (stimulation of both sympathetic and parasympathetic activity) and endocrine changes (hyperglycaemia, hyperkalaemia, release of pituitary hormones) which, although they may be influenced by the convulsive activity, appear to arise primarily through the direct effect of neuronal discharges in the hypothalamus.

Table II lists physiological measures of the response to the first treatment of a course of ECT which have been investigated as potential predictors of outcome. Most attention has been directed to the measurement of seizure activity itself because it has been possible to measure the electrical activity of the brain with EEG for over 50 years and most theories concerning the mode of action of ECT consider cerebral seizure activity to be an essential component of effective treatment (Kendell, 1981).

**TABLE II**

Biological measures of the consequences of ECT investigated as potential predictors of recovery

<table>
<thead>
<tr>
<th>Measure</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure activity</td>
<td>(Ottosson, 1962)</td>
</tr>
<tr>
<td>Seizure threshold</td>
<td>(Sackheim et al., 1987a)</td>
</tr>
<tr>
<td>Autonomic changes</td>
<td>(Prudic et al., 1987)</td>
</tr>
<tr>
<td>Monoamines and metabolites</td>
<td>(Guze et al., 1956)</td>
</tr>
<tr>
<td>Post-seizure electroencephalogram</td>
<td>(Pink, 1979)</td>
</tr>
<tr>
<td>Pituitary hormones</td>
<td>See below</td>
</tr>
</tbody>
</table>
Methodological problems in studies of potential predictors

Patient selection

Early attempts to identify biological predictors of outcome often included patients suffering from schizophrenia and neurotic conditions as well as patients suffering depressive illness. Although it was a legitimate concern to investigate indications for ECT in such illnesses (Fink, 1979), Hamilton (1986) has pointed out the implications of this. Many of the correlates of recovery were simply characteristics of depressed patients (who respond well to ECT) as opposed to schizophrenic patients or neurotic patients (who respond more slowly or not at all). The depressed patients in such studies tended to be older than the other patients included, yet the effects of age on physiological responses were not considered, for example, in the Funkenstein test (see below).

Early studies not only included patients with a variety of psychiatric illnesses, but also a range of depressive syndromes - most of which are no longer treated by ECT. This review concentrates on studies which use reliable operational definitions of depressive illness, although earlier studies will be included to illustrate the variety of biological measures investigated.

Lack of control groups

No studies of potential clinical or biological predictors of recovery after ECT have included a comparison group of patients who receive no treatment at all and few studies have considered a comparison group of
patients who received placebo or antidepressant drugs. Thus, we do not know if putative predictors are markers of a specific response to ECT alone rather than markers of the likelihood of spontaneous recovery or a good response to any physical treatment for depressive illness. Indeed Hobson (1953) noted the similarity between the clinical features he associated with recovery after ECT and those already noted to be associated with a favourable outcome of depressive illness before ECT was available.

The clinical predictive scale devised by Carney et al., (1965) has been reported to be of high predictive accuracy in contemporary practice of ECT (Katona & Aldridge, 1984), although this was not confirmed in the study by Crow et al. (1984) - one of the few studies which included a comparison group of patients who were given simulated ECT. There are 10 clinical features in the scale, five of which are reported to correlate with a good outcome (weight loss, pyknic body build, early morning wakening, somatic or paranoid delusions) and five features associated with a poor outcome (anxiety, worsening of mood in the afternoon, self-pity, hypochondriasis, hysteria) at six months after ECT. Later work from this same research group showed that three of these features (anxiety, hypochondriasis and hysteria) are correlated with a poor long-term (average 3.8 years) outcome among patients admitted to hospital suffering from either anxiety states or depressive illness (Kerr et al., 1972), and, more specifically, depressive illness itself (Kerr et al., 1974) irrespective of the treatment received. Weight loss and early morning wakening were associated with a good long-term outcome in depressive illness (Kerr et al., 1974), irrespective of the treatment given. This lack of distinction between markers of spontaneous
recovery, a good response to any physical treatment, and a good response to ECT itself is more significant today now that drug treatments for depressive illness are more widely available and many patients treated by ECT have already failed to respond to antidepressant drugs.

Definition of recovery

There are important theoretical and practical difficulties in the measurement of clinical outcome after ECT. There is no agreed definition of recovery after ECT. Table III lists a variety of the methods of assessment and definitions of recovery which have been used in ECT studies. Also included for comparison is the definition of recovery from depressive illness which has been developed in the National Institute of Mental Health (NIMH) Collaborative Study on the Psychobiology of Depression (Keller et al., 1982). Many studies fail to distinguish between improvement and recovery. Often depressed patients who are treated by ECT are severely ill and it would seem likely that a significant proportion will improve considerably and yet still have residual symptoms, that is, fail to return to a normal state of health. Secondly, there is no agreement about what degree of improvement constitutes a good response, nor about the definition of recovery. Most ECT studies have used a less rigorous definition of recovery than that developed in the NIMH programme. This may be one important reason that the rates of recovery reported in ECT studies are higher than the rates of recovery observed in the NIMH longitudinal study of the process of recovery from depressive illness (Keller et al., 1982). Thirdly, there is no agreement about the timing of assessment. In studies which report high rates of improvement or recovery, the assessment has been made.
### Table III

Method of assessment of recovery from depressive illness after ECT

<table>
<thead>
<tr>
<th>Authors</th>
<th>Timing of assessment</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hobson (1953)</td>
<td>2 weeks after end of ECT</td>
<td>Good improvement = completely free of symptoms or only slight residual symptoms which would not interfere with work or social relationships.</td>
</tr>
<tr>
<td>Roberts (1959)</td>
<td>1 &amp; 3 months after end of treatment</td>
<td>Good result = less than 5 on modified HRSD&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ottosson (1962)</td>
<td>1 week after 4th treatment &amp; 1 week after end of treatment</td>
<td>Global improvement score &amp; symptom change score &amp; number of ECT</td>
</tr>
<tr>
<td>MRC (1965)</td>
<td>After 4 weeks of treatment</td>
<td>Recovery = no or few symptoms (doctors' assessment)</td>
</tr>
<tr>
<td>Carney et al. (1965)</td>
<td>Discharge, 3 months &amp; 6 months later</td>
<td>Satisfactory outcome = symptom-free with full social recovery or full social recovery with residual symptoms</td>
</tr>
<tr>
<td>Keller et al. (1982)</td>
<td>8 weeks after ECT</td>
<td>Recovery = no residual symptoms or only one or two symptoms in mild degree for 8 consecutive weeks</td>
</tr>
<tr>
<td>Crow et al. (1984)</td>
<td>After 1, 2, 3 &amp; 4 weeks of treatment; 1 &amp; 6 months after completion</td>
<td>Improvement in HRSD score (definition of recovery not given)</td>
</tr>
<tr>
<td>Lipman et al. (1986b)</td>
<td>6 months after discharge</td>
<td>Successful = BDI&lt;sup&gt;b&lt;/sup&gt; less than 20; &amp; 50% less than before treatment; no readmission to hospital</td>
</tr>
<tr>
<td>Decina et al. (1987)</td>
<td>After completion of ECT</td>
<td>Successful response = 50% reduction in HRSD</td>
</tr>
<tr>
<td>Katona et al. (1987)</td>
<td>1-2 weeks after ECT</td>
<td>HRSD. Good outcome = no evidence of significant residual depression; Good outcome = no evidence of relapse on casenote review</td>
</tr>
</tbody>
</table>

<sup>a</sup> Hamilton Rating Scale for Depression (Hamilton, 1960)

<sup>b</sup> Beck Depression Inventory (Beck et al., 1961)
immediately after the course of ECT (Andrade et al., 1988) or within a few weeks of the end of the course (MRC, 1965). There is a greater variability of outcome as the length of follow-up is extended. Recent outcome studies have found that less than one third of patients remain well six months after ECT (Coryell & Zimmerman, 1983; Lipman et al., 1986b; Katona et al., 1987). It is not clear to what extent this is because of relapse, that is the return of symptoms of the index illness, or recurrence, that is the emergence of depressive symptoms which constitute a new episode of illness.

When follow-up is extended beyond the period of hospital stay, the method of assessment may be unsatisfactory; for example, some recent outcome studies have relied on follow-up by telephone. Despite these methodological difficulties, there is general agreement that the majority of patients with typical depressive illness do well in the short term after ECT.

In conclusion, the definition of recovery and the time assessment is made are important influences on the results of ECT studies and clearly merits further study. Future ECT studies should distinguish between improvement and recovery and assess patients at more than one time point after the course of ECT.
Review of biological measures made before ECT

Resting EEG

Soon after the introduction of ECT, it was discovered that the EEG record changed markedly after a course of treatment (Fink, 1979). This led to many investigations of the relationship of EEG changes to outcome and cognitive side-effects.

There is a higher prevalence of abnormal activity on the EEG amongst patients receiving ECT than in the general population (Mosovich & Katzenelbogen, 1948; Kennard & Willner, 1948). These abnormalities are more likely in older patients but show no relationship to clinical diagnosis or particular symptoms of depressive illness. Some studies have found that patients with a normal (alpha) EEG record have a better outcome than patients with abnormal tracings but this has not always been replicated (Fink, 1979).

Sedation Threshold

Shagass (1954) hypothesized that 'emotional arousal' was related to clinical diagnosis and measured this by giving sodium amytal intravenously until the EEG showed an increase in beta activity and this point was defined as the sedation threshold. Patients with low thresholds were usually suffering from psychosis and had a good prognosis with ECT. The inter-rater reliability of the test was low (Thorpe, 1962) and its usefulness as a predictor was not confirmed (Roberts, 1959).
Sleep EEG

The most consistent abnormality in the sleep of depressed patients is a reduction in the time between sleep onset and the first period of rapid eye movement (REM) sleep (see Rush et al., 1986 for review). If the reduction in REM latency is closely correlated with the presence of depressive illness, then this measure may be useful in the selection of patients to receive ECT. Early studies on the effects of ECT on the sleep EEG were difficult to interpret because of small sample sizes or because of mixed diagnostic samples (see Hoffman et al., 1985.) A pilot study in 10 depressed patients suggested that serial sleep EEGs could monitor recovery from depressive illness during a course of ECT (Grunhaus et al., 1985). However, subsequent studies in larger samples of depressed patients have only confirmed that several factors confound the relationship between shortened REM latency and the likelihood of recovery during a course of ECT. Although the studies of Hoffman et al. (1985) and Grunhaus et al. (1988) have found a trend for REM latency to increase during a course of ECT, Coffey et al. (1988) found that individual patients showed marked variability in REM latency both during and after the course of ECT. Moreover, Hoffman et al. (1985) found that REM latency could return to normal values without any clinical improvement in depressive illness and Coffey et al. (1988) found that clinical improvement could occur in the continued presence of shortened REM latency. Indeed, shortened REM latency may persist for up to six months after recovery from depressive illness (Rush et al., 1986).

Despite much contemporary enthusiasm for the study of abnormalities of sleep occurring during depressive illness, there is no evidence to
suggest the presence of these abnormalities will help to select patients who will recover after ECT.

**Autonomic reactivity**

The study of the effects of mental illness on the autonomic nervous system began early in the 20th century and was one of the first systematic approaches to the study of the constitutional aetiology of mental illness (Rose, 1962). The Funkenstein test (Funkenstein et al., 1948) measured the changes in blood pressure to injected adrenaline and methacholine. Patients in whom a chill developed after methacholine and patients in whom blood pressure rose more than 50 mm Hg after adrenaline and had a sustained fall of blood pressure after methacholine injection were reported to improve after ECT. Although reviewers suggested the test merited further development (Rose, 1962; Thorpe, 1962), they also criticized it adversely because of its low reliability, its uncertain physiological significance and its failure to take account of the effects of age. Despite the cautious enthusiasm of reviewers, the test fell from favour because other researchers failed to confirm the predictive accuracy of the test (for example, Roberts, 1959).

A recent study in six geriatric depressed patients suggested that the morning fall in systolic blood pressure on standing was correlated with the extent of eventual improvement in depression after a course of ECT (Stack et al., 1983). As might be predicted from the early work on autonomic reactivity, there was considerable variability from day to day in the fall in blood pressure. The finding requires confirmation in a larger sample.
Monoamines and metabolites

The catecholamine hypothesis of depressive illness (Schildkraut, 1965) arose from the observations that drugs causing depletion of brain noradrenaline produced depression, and drugs that increased or potentiated brain noradrenaline alleviated depression. Contrary to the original hypothesis, depressed patients often have increased plasma catecholamine concentrations. It has been suggested that the increase in plasma catecholamine concentration is associated with a vulnerability to stress (Cooper et al., 1985) or anxiety (Wyatt et al., 1971) or typical features of depressive illness (Roy et al., 1985). No relationships have been reported between baseline plasma catecholamine concentrations and clinical outcome after ECT.

3-methoxy-4-hydroxyphenylglycol (MHPG) is believed to be the principal metabolite of central nervous system (CNS) noradrenaline and may be measured in urine. Although urinary MHPG is less among depressed patients who receive ECT than in controls (Joseph et al., 1985) there is no relationship between the clinical response after ECT and the urinary excretion of MHPG (Joseph et al., 1985; Sharma et al., 1986), nor cerebrospinal fluid (CSF) concentrations of the metabolites of dopamine, serotonin (Hoffman et al., 1985; Aberg-Wistedt et al., 1986), and noradrenaline (Aberg-Wistedt et al., 1986).

The concentration of monoamine metabolites may be affected by alterations in the activity of monoamine oxidase (MAO). Although there are
no data on the effects of ECT on the activity of MAO in the CNS; MAO activity in platelets is unaffected by ECT (Moriarty et al., 1987).

**Calcium**

The introduction of lithium increased interest in the study of mineral metabolism during depressive illness. Depressive illness is associated with an increase in intracellular sodium and water which returns to normal on recovery (see Fink, 1979, for review). Ottosson (1974) has argued that the changes in sodium, potassium and water metabolism are secondary to recovery from depression and are not a direct effect of ECT because a similar normalization is seen during recovery in patients given other physical treatments for depressive illness. Since disturbance of calcium metabolism (particularly in parathyroid disorders) is associated with mood disorder, there has been much interest in calcium metabolism during recovery from depressive illness. Successful treatment of depressive illness by either imipramine or ECT is associated with decreased urinary excretion of calcium (Flach, 1964) and a positive calcium balance (Fragalla & Flach, 1970). A single ECT has no effect on the concentration of total or ionized calcium in plasma (Malleson et al., 1968). Carman et al. (1977) found that calcium concentrations fell in both the CSF and serum after a successful course of ECT in seven severely depressed patients, and reviewed mechanisms by which calcium might alter mood. However, this finding was not confirmed in a larger study of 20 patients treated by ECT (Mellerup et al., 1979).

Intracellular ionized calcium alters the activity of a wide range of intracellular enzymes which may be of relevance to the pathology of — 24 —
depressive illness (see Meltzer, 1986; for review). Since the active transport of calcium across membranes is mediated by calcium-dependent adenosinetriphosphatase (Ca-ATPase), there has been interest in the study of the effects of ECT on the activity of this enzyme. The results, however, are conflicting. For example, Choi et al. (1977) found that the activity of Ca-ATPase on red blood cells rose after a course of ECT in 11 depressed women, whereas Whalley et al. (1980) were unable to confirm this finding in a sample of 12 unipolar depressed patients. This discrepancy may be at least in part explained by the fact that all the patients in the study by Whalley et al. were of unipolar type, whereas five of the patients in the study by Choi et al. suffered from bipolar illness. A recent study by Bowden et al. (1988) has shown that unipolar and bipolar depressed patients differ in several measures of calcium metabolism and in the activity of Ca-ATPase in both platelets and erythrocytes.

Calcium metabolism is of considerable theoretical importance in attempts to understand the pathology of affective illnesses. However, the dynamics of calcium metabolism during ECT are complex. Evidence from the effects of repeated ECS in rats suggests that the production of CSF, the distribution of calcium between blood and CSF, and the distribution of calcium between CSF and brain are altered (Barkai & Nelson, 1987). These changes may yet prove to be of theoretical importance, but there is no evidence that serum or CSF calcium concentrations before ECT are useful predictors of outcome.
Cortisol

Increased activity of the hypothalamic-pituitary-adrenocortical (HPA) axis is common in depressive illness. Early studies were concerned with cortisol release as a potential biological measure of psychological stress. Elevated cortisol concentrations have been reported in the plasma (Gibbons, 1964), urine (Carroll et al., 1976a) and CSF (Carroll et al., 1976b) of depressed patients. Raised plasma cortisol concentrations are found in several psychotic illnesses and are not specific for severe depressive illness (Christie et al., 1986). Serum cortisol concentrations are weakly correlated with the severity of depression (Whiteford et al., 1987), but there is no relationship between serum cortisol concentration before ECT and recovery from depression after ECT (Deakin et al., 1983).

Endocrine challenge tests

Endocrine challenge tests are used in two ways in ECT research. Patients who respond rapidly to ECT may have a common physiological abnormality identified by a specific pattern of endocrine dysfunction (Fink, 1979). The two most common endocrine challenge tests used to test this hypothesis are the dexamethasone suppression test (DST) and the thyrotrophin releasing hormone (TRH) stimulation test. Secondly, neuroendocrine tests may be used to assess monoamine neurotransmitter function in depressed patients (Checkley, 1980). Such tests make use of the role of monoamines in the control of the release of anterior pituitary hormones. The radioimmunoassay (RIA) for growth hormone (GH)
is widely available and has enabled the control of the release of GH to be studied in detail.

**DST** Another feature of the increased activity of the HPA axis common in depressive illness is a resistance to normal feedback inhibition on the release of cortisol. Indeed Carroll et al. (1981) recommended that resistance of the HPA axis to dexamethasone was a specific laboratory test for depressive illness; they argued that the DST revealed abnormal function in the limbic system and hypothalamus. Previous studies by this group had suggested that during successful treatment of depressive illness the DST gradually approaches normal values (Carroll et al., 1976c). In the largest early study of depressed patients treated by ECT, Coryell (1982) found that patients in whom dexamethasone failed to suppress cortisol release in the DST (that is DST non-suppressors) had a better outcome on global ratings than DST suppressors on global ratings (but not final score on the HRSD). Other small studies found that early normalization of the DST (by the fourth to sixth treatment) was predictive of a good clinical response. Those patients in whom the DST failed to normalize had a poor clinical outcome (Dysken et al., 1979; Greden et al., 1980; Albala et al., 1981; Papakostas et al., 1981).

Subsequent studies have challenged these early findings. In a study of nine patients Decina et al. (1983) showed that serum cortisol concentration after dexamethasone was greater during and immediately after a course of ECT than before ECT. The increase in cortisol release was independent of clinical response to ECT. Five further studies have investigated the value of the DST as a predictor of the short-term
outcome after ECT in a total of 154 depressed patients (Katona & Aldridge, 1984; Lipman et al., 1986a; Modai et al. 1986; Devanand et al., 1987; Fink et al., 1987). Each of these studies uses an operationally defined group of depressed patients, comparable definitions of DST non-suppression and categorizes patients by outcome. There was no evidence in any single study that DST status immediately before ECT was predictive of short-term outcome after ECT. Overall the predictive accuracy of DST non-suppression was 53%. Four subsequent studies have investigated the relationship between DST status and clinical outcome six months after treatment with ECT in a total of 130 depressed patients (Coryell & Zimmerman, 1983; Lipman et al., 1986b; Fink et al., 1987; Katona et al., 1987). There was no difference in outcome between initial DST suppressors and non-suppressors. The first two studies found that persistent non-suppressors had a better clinical outcome than did the initial non-suppressors who became suppressors after ECT, but this finding was not confirmed by the later studies. A confounding factor, however, was that the timing of the final DST was not standard.

These results may seem disappointing in view of early enthusiasm about the value of the DST as a predictor of clinical response to antidepressant treatment. A review by Arana et al. (1985) concluded that the response to anti-depressant treatment in depressed patients who are DST non-suppressors is only slightly better than in those who are suppressors. Coryell (1986) suggested that the effect of ECT on the diencephalon may invalidate the DST as a marker of clinical response. Lipman et al. (1986b) supported the view of Abrams (1982) who felt that once depressed patients were selected for ECT, there was not enough variability among them to predict outcome. Certainly, patients selected
for ECT are not typical of the range of depressed patients, for example; they have a higher prevalence of psychosis and suicidal intent, and many will have failed to respond to antidepressant drugs. Patients included in studies involving the DST are even more highly selected because patients with significant weight loss, physical illness, personality disorder and substance abuse are excluded. Contemporary studies of drug-free depressed patients selected for ECT show that the vast majority (90%) are DST non-suppressors (Grunhaus et al., 1987).

Interest has now shifted to investigate the usefulness of serial DSTs as a way of monitoring the process of recovery during a course of ECT (Coryell, 1986; Grunhaus et al., 1987; Varma et al., 1988). The findings of these studies are in general agreement. When the mean post-dexamethasone plasma cortisol concentration for a sample of patients is plotted against mean score on depression rating scales at several points throughout a course of ECT, then as plasma cortisol concentration falls, so does the severity of depression. As Gibbons & Davis (1984) have pointed out, the mean values of two variables which are measured repeatedly tell us little, if anything, about longitudinal relationships. An alternative strategy is to plot the repeated measures of the two variables for individual patients. When such data are made available (Grunhaus et al., 1987), it is clear there is considerable variation among patients in the patterns of association between post-dexamethasone plasma cortisol concentration and the severity of depressive illness.

The DST is a relatively simple endocrine challenge test which has been of great appeal to psychiatry - over 10,000 patients have been studied in recent years (Arana et al., 1985). Despite its appeal, it
does not identify which patients among those suffering depressive illness will recover successfully after a course of ECT. It is yet to be established that the DST can monitor the process of recovery during a course of treatment.

TRH stimulation test In 1972, two groups reported that a proportion of depressed patients have a blunted thyroid stimulating hormone (TSH) response to TRH (Prange et al., 1972; Kastin et al., 1972). Those reports stimulated a search for changes in the TRH stimulation test during treatment. Most of this work concerned treatment with antidepressant drugs, but Coppen et al. (1980b) reported that there was a non-significant reduction in the TSH response to TRH in five patients after ECT. They did not report any association between TSH release before ECT and outcome. Papakostas et al. (1981) tested seven patients before and after ECT and found no relationship between the TRH test and clinical outcome; however, as the authors admitted, their sample was too small to draw firm conclusions.

Later work from Kirkegaard's group in Copenhagen switched emphasis from the prediction of recovery from depressive illness after ECT to the prediction of relapse after successful ECT. Krog-Meyer et al. (1984) measured the maximum increase in TSH after TRH before and after a successful course of ECT given to 39 unipolar depressed patients. Their findings suggested that continuing remission in the six months after successful ECT was more likely in those patients in whom the maximum release of TSH after TRH increased by at least 2μu/ml over the course of ECT. The predictive value of changes in the TRH stimulation test was not confirmed by Decina et al. (1987) Only two of the 23 depressed patients
showed any increase in the release of TSH after a course of treatment and in 20 patients the release of TSH decreased after TRH. No patient showed an increase in the release of TSH that reached at least 2μu/ml despite the fact that nine of the patients were recovered after ECT and that in seven of these nine patients the remission was maintained for at least one year. Before ECT, there was no difference between the responders and non-responders in mean TSH response to TRH.

Decina et al. (1987) suggested that a confounding factor in the interpretation of the TRH stimulation test may be that ECT itself leads to an increase in the release of endogenous TRH. They suggested that this increase in TRH during a course of ECT may lead to down-regulation of pituitary TRH receptors which would make the gland less responsive to exogenous TRH. Certainly, there is evidence in rats that ECS leads to sustained elevations of TRH in the forebrain (Sattin et al., 1987). Kirkegaard & Faber (1986) suggested another confounding factor was an increased serum concentration of free thyroxine during depressive illness. Muller & Boning (1988) have shown that remission from both mania and depression is associated with a decrease in serum thyroxine which was not accompanied by a reduction in serum TSH.

The TRH stimulation test may be useful in research to detect physiological changes during a course of ECT, but interpretation of the serum TSH concentration is complicated by several factors. The test has not been shown to identify depressed patients who will recover with ECT.

Neuroendocrine tests of monoamine function Most of the laboratory research on the mechanism of action of ECT has focussed on changes in
monoamine neurotransmitter function that occur in rodents exposed to repeated ECS. Much of the early research was concentrated on changes in the activity of the classical monoamines 5-hydroxytryptamine (5-HT), dopamine and noradrenaline (Grahame-Smith et al., 1978). Recent laboratory research has concerned the effects of ECS on specific receptor types, for example, beta-adrenoceptors, alpha-2-adrenoceptors, type B receptors for gamma-aminobutyric acid (Green, 1987), and sub-classes of receptors for 5-HT (Goodwin et al., 1985; Green, 1987). Studies in human beings have been limited to the use of drugs which stimulate specific monoamine systems leading to hormone release from the pituitary. As noted above, the release of GH from the anterior pituitary has received most attention (Cowen, 1986). Although there is evidence from animal studies that repeated ECS results in functional changes in brain monoamine neurotransmission, studies in depressed human beings have produced conflicting results. Neuroendocrine responses are complex and there are many steps between the administration of a drug and the measurement of hormone release in plasma. Three drugs which release GH have been used in challenge tests in depressed patients receiving ECT, clonidine (alpha-2 agonist), apomorphine (dopamine agonist), and amphetamine (non-specific monoamine agonist). Although Costain et al. (1982) found a significant increase in the GH response to apomorphine after a course of ECT (thus supporting the hypothesis that ECT produces an enhancement of dopamine-mediated responses in the brain), this finding was not confirmed by Christie et al. (1982). Costain et al. (1982) noted that they had excluded from their own study patients with a high basal concentration of GH. When such patients were included in the analysis, the increase in apomorphine response following ECT was no longer significant. Slade & Checkley (1980) found no change in the
release of GH by either clonidine or methyl-amphetamine in depressed patients after a course of ECT.

Plasma prolactin concentration is increased by the administration of TRH which may be mediated by 5-HT-containing neurones. Coppen et al (1980a) found that prolactin release after TRH was increased after ECT; however, there was no association between prolactin release before ECT and clinical recovery. The release of prolactin may be inhibited by apomorphine, which is thought to be mediated by dopamine-containing neurones. Balldin et al (1982) found that a course of ECT enhanced the inhibition of the release of prolactin by apomorphine. There were no correlations between serum prolactin concentrations before or after apomorphine and clinical recovery after ECT.

The interpretation of the results of such challenge tests is complex. For example, the release of GH is influenced by age, ovarian function, time of day, meals, baseline concentration, alcohol and concomitant psychotropic drug therapy (Checkley, 1980). Specific agonists or antagonists to monoamine receptors in the CNS may be of value in research, but with interpretation confounded by so many variables, they have no established role in clinical practice.

Binding of tritiated imipramine by platelets

Tritiated imipramine binds at a site which is thought to be closely associated with, but not identical to, the 5-HT uptake site in platelets and in the brain (Wagner et al., 1987). Bech et al. (1988) have listed a number of studies which reported that the maximum binding (Bmax)
of tritiated imipramine was reduced in platelets from depressed patients when compared with platelets from controls. Although the difference between depressed patients and controls was small and there were studies which failed to confirm a difference, the binding of tritiated imipramine has been investigated as a possible biological marker of depressive illness. Langer et al. (1986) reported that the Bmax value of tritiated imipramine rose after a successful course of ECT in six depressed patients. Maj et al. (1988) criticize this finding because patients were prescribed antidepressant drugs and/or lithium carbonate by the time of re-testing. Their own study of 15 depressed patients who received only benzodiazepine drugs between testing did find an increase in Bmax after a course of ECT. The patients in this study, however, may have received antidepressant drugs up to 12 days before the start of ECT. Neither study reported an association between the Bmax of tritiated imipramine and outcome after ECT. The World Health Organisation pilot study of the platelet imipramine receptor (Bech et al., 1988) questioned the validity of the receptor as a biological marker of depressive illness; controlled trials in three centres failed to confirm any difference between depressed patients and controls and noted that the confounding effects of tricyclic antidepressants on the binding sites may have explained the findings of earlier studies.
Review of biological measures of the consequences of ECT

Seizure activity

There is a general belief that cerebral seizure activity is the "crucial ingredient" of ECT (Kendell, 1981). The first line of evidence in support of this belief is derived from studies which compare the antidepressant effects of real ECT with those of simulated ECT (where all stages of preparation and anaesthesia for ECT are carried out bar the passage of an electric stimulus). Thus the additional antidepressant effects of the seizure can be compared with the non-specific therapeutic effects of simulated ECT, for example, the respite of hospital admission and medical and nursing attention. Most reviewers (for example, Fink, 1979; Kendell, 1981) conclude that the antidepressant effect of the seizure has been established. Crow & Johnston (1986) have listed the methodological shortcomings of many of these comparative studies; although they conclude that patients treated by real ECT do improve to a greater extent than those receiving simulated ECT, the difference is temporary, and is not apparent one month after the end of a course of ECT. The second line of evidence is that seizures induced by inhalation of the convulsant ether flurothyl have similar antidepressant effects to electrically induced seizures (see Fink, 1979, for review). None of these studies included a comparison group of depressed patients treated by placebo or simulated ECT. The third line of evidence is the seminal work of Ottosson (1960; 1962). Ottosson demonstrated that seizures shortened by the administration of lidocaine were less efficient in relieving depressive illness than self-limited grand mal seizures. It is less commonly repeated that Ottosson (1962) found that the duration
of the grand mal seizure had no significant relationship to therapeutic efficiency:

"It seems, therefore, to be of no importance whether a person develops long or short grand mal seizures; the essential thing being that they are grand mal self-limited seizures."

There may be a range of electrophysiological response to ECT from the so-called "missed seizure" where there is a failure to induce any seizure activity, through types of minor seizure similar to petit mal, to classical tonic clonic (grand mal) generalized activity (Small et al.; 1978). There is rough agreement about what constitutes an adequate tonic clonic seizure. The proposed definitions vary with the method used to monitor seizure activity, namely, 30 seconds of generalized convulsive activity (d'Elia et al., 1983), 25 seconds of convulsive activity in a forearm isolated from the muscle relaxant by a tourniquet (Fink, 1979), or 30 seconds of seizure activity on EEG (Fink, 1979). The American Psychiatric Association (1978) recommended that "a seizure lasting less than 25 seconds may not be adequate"; observation alone, the tourniquet method and EEG monitoring were all practical methods to ensure seizures were adequate.

There is only circumstantial support for these definitions. For example, several authorities cite the work of Small et al. (1978) as support for a minimum seizure duration of 25 seconds. In fact, these authors did not define an adequate seizure but noted that minor seizures tended to last less than 25 seconds, and were not followed by electrical
silence or a phase of delta wave activity on EEG. There is now good evidence that there is no relationship between individual seizure length (measured by observation or EEG) and recovery after a course of ECT (Weiner et al., 1983; Rich & Black, 1985; Zorumski et al., 1986).

Studies which purported to find a relationship between cumulative seizure duration and clinical improvement (for example, Maletzky, 1978) did not take into account the relationship between the number of ECT given and clinical improvement.

It may not be feasible to define a minimum length for a therapeutic seizure as time alone takes no account of the degree of spread of seizure activity over the cortex or throughout the brain. Seizure generalization may be an important influence on the therapeutic efficacy of induced seizures (Daniel, 1983). Clearly this is an area which merits further research.

In conclusion, it is important to ensure that a generalized tonic clonic (grand mal) seizure occurs at each ECT treatment. The induction of satisfactory cerebral seizures does not, however, guarantee that a course of ECT will be successful. There is no correlation between the length of convulsive or cerebral seizure activity and clinical outcome.

Seizure threshold

The traditional view of the goal of ECT is that it is to elicit a generalized tonic clonic seizure of adequate duration, delivering the
minimum possible intensity of electrical current. This recommendation
derives from research suggesting that the antidepressant effects of ECT
are tied to seizure elicitation, whereas increasing the stimulus
intensity produces unnecessary cognitive side-effects (for example,
Ottosson, 1960). Seizure threshold, defined as the minimum electrical
stimulus necessary to elicit adequate generalized seizures, varies 12-
fold among drug-free depressed patients (Sackeim et al., 1987a). The
practical implication of this finding is that in fixed stimulus ECT,
patients with a low seizure threshold can receive electrical stimuli many
times greater than that necessary to elicit a generalized seizure which
may increase the degree of cognitive side-effects substantially.
Patients with a high seizure threshold will have shorter seizures than
patients with a low threshold (Sackeim et al., 1987b). This led
Sackeim and colleagues to investigate the relationship between seizure
threshold at the start of a course of ECT and clinical outcome. Non-
responders to bilateral ECT had a mean seizure threshold almost twice
that of responders, although the overlap was not given. There was no
difference in seizure threshold between responders and non-
responders to titrated right unilateral ECT (Sackeim et al., 1987b). The efficacy of
titrated ECT (that is, the use of the minimum electrical stimulus to
elicit a generalized seizure) has not been assessed.

Devanand & Sackeim (1988) reported the case of a depressed patient
in whom the administration of intravenous lidocaine before ECT to prevent
ventricular arrhythmia resulted in the failure to elicit a seizure at a
stimulus intensity much greater than that required at previous and
subsequent treatments. A similar finding was reported in a middle-aged
depressed woman (Hood & Mecca, 1983). Both sets of authors suggested
that lidocaine increased the seizure threshold, a finding not detected by Ottilsson because the electrical stimuli he used were far in excess of the seizure threshold. Furthermore, they offered an alternative explanation for the reduced antidepressant effect of lidocaine-modified seizures, namely, that lidocaine increased the seizure threshold; they argued that stimulus intensity does contribute to the antidepressant effect of ECT because of the evidence from their own work that generalized seizures induced by an electrical stimulus just in excess of the seizure threshold have less of an antidepressant effect than those induced with more energetic stimuli. They also cited the work of Robin & De Tissira (1982) who found that bilateral ECT using high energy electrical stimuli was more effective than bilateral ECT with low energy stimuli. They concluded that although a generalized seizure was a necessary component of successful ECT, it was not sufficient in itself and the degree to which stimulus intensity exceeds seizure threshold is also an important influence on the antidepressant effect of induced seizures.

The strength of this argument will be weakened if it can be shown that the seizures induced by low energy brief pulse stimuli are shorter or less well generalized than seizures induced by higher energy stimuli because this would imply that it was the reduction in quantity or quality of seizure activity which led to the reduced antidepressant effect. Robin & De Tissira (1982) assessed seizure activity by the observation of tonic clonic muscle activity and Sackeim et al. (1987c) used single channel EEG recording. Although both groups stated that the duration of seizures induced by low and high energy stimulation was the same, neither of these methods can estimate seizure generalization which may be an
important influence on the antidepressant effect of induced seizures (Daniel, 1983).

In conclusion, although the predictive accuracy of seizure threshold at the first ECT has not been established, the interaction of seizure threshold, stimulus intensity and seizure generalization on outcome and cognitive side-effects clearly merit further study.

Autonomic changes

Cardiovascular changes at the time of ECT may give information about the reactivity of the sympathetic nervous system. Prudic et al. (1987) studied 34 depressed patients throughout a course of ECT and found no cumulative pattern in either heart rate or blood pressure after treatment. Cardiovascular changes were not related to treatment or outcome variables and it seemed that only age and the heart rate before ECT were predictive of cardiovascular change.

Monoamines and metabolites

The work of Funkenstein and colleagues (see above) stimulated interest in other means of study of sympathetic nervous activity. Weil-Malherbe (1955) found that ECT increased plasma concentrations of adrenaline and noradrenaline, a finding confirmed by Havens et al. (1959). Although heightened sympathetic activity accompanied seizures, this was not essential to treatment outcome as the injection of barbiturate suppressed this response without reducing therapeutic efficacy. Moreover, the successful ECT treatment of a depressed patient who had previously had a
bilateral adrenalectomy suggested that the adrenals were not essential to the therapeutic process (Guze et al., 1956).

Post seizure EEG

During a course of ECT, the interictal EEG shows progressive reduction of the mean frequency and an increase in the mean amplitude. The degree of slowing is related to the number and frequency of seizures and, to a lesser degree, the type of currents and placement of electrodes (Fink, 1979; Small et al., 1978). Fink has argued that the amount of slow-wave activity is not linearly related to clinical outcome, but that its early appearance and persistence is a necessary condition for improvement. There is, however, great variability among patients in the amount, rate and persistence of EEG slowing after ECT. Studies which have investigated the predictive utility of interictal EEG have found that EEG slowing only becomes prevalent after the third treatment and thus would be more appropriate for predicting the end-point of a course of treatment rather than predicting its likely success at the outset.

Roth et al. (1957) developed a technique for evaluating the EEG changes produced by ECT based on measurements of delta activity after injection of a standard amount of sodium thiopentone within 3-4 hours after a fit. Roth and colleagues were able to detect EEG slowing at an earlier stage of treatment than in the resting interictal EEG. They found a relationship between the thiopentone-induced EEG slowing and relapse at three and six months after the end of treatment, but concluded that thiopentone-induced delta activity had only a weak relation to the immediate outcome of ECT.
Recent studies have compared unilateral and bilateral ECT in their effects on the symmetry of EEG changes such as the appearance of spikes and sharp waves or slow waves on the EEG after a course of ECT (Stromgren & Juul-Jensen, 1975; Abrams et al., 1987). After a course of ECT there is a tendency for unilateral ECT to be associated with changes over the stimulated hemisphere and for bilateral ECT to be associated with changes over the left hemisphere. The significance of these findings to either the mode of action or cognitive side-effects of ECT has yet to be established as between one-third and one-half of patients do not develop any asymmetry in the EEG.

Release of pituitary hormones after ECT

Background

The effects of ECT on the function of the pituitary have been studied extensively and there are several reasons for this interest. It has long been recognized that endocrine disorders can be accompanied by prominent mental abnormalities, especially in thyroid disease and Cushing's syndrome (Lishman, 1987). After the introduction of ECT, the effects of the treatment on temperature control, appetite, weight and autonomic activity aroused interest in the role of the hypothalamus in the mode of action of ECT (Fink, 1979). As noted above, hormone release (particularly of cortisol) has been investigated as a potential biological measure of psychological stress and abnormalities in the function of the HPA axis are common among depressed patients. Neurotransmitters implicated in the pathology of depressive illness are involved in the regulation of the HPA axis (Whalley et al., 1987). Akiskal & McKinney (1975) have proposed
that abnormal function in the diencephalon may be "the final common pathway" in the aetiology of depressive illness, that is, the culmination of processes converging on those areas of the diencephalon which modulate arousal, mood, motivation and psychomotor function and leads to the typical symptoms of depressive illness. Much of what we know about the biochemical effects of repeated seizures is derived from the effects of ECS on rodents (Green & Nutt, 1987). The study of ECT's effects on hypothalamic-pituitary activity is one way in which hypotheses developed in laboratory animals can be tested in depressed human beings treated by ECT.

Issues

A stimulus is an influence that stimulates, increases or quickens the function of an organ (Oxford English Dictionary, 1979). There are many types of stimuli which influence the release of pituitary hormones (see Rose, 1984, for review). Thus pituitary hormone release can be a response, or an answer, to a stimulus and this response can be measured. When the stimulus is novel, strange or unfamiliar, the term 'stress' is used for the stimulus (Rose, 1984), although the definition of stress in research on human beings has been much debated. The NIMH working group recommended that such research must take into account the appraisal of the stimulus by the individual and the individual's coping style (Eichler et al., 1986). A yet more narrowly defined definition of stress has been suggested by Katkin (1986); he recommended that the term stress be used only for stimuli which lead to overt behavioural change which impairs performance, alters experience (for example, dysphoria), or causes inappropriate physiological responses. In research on the effects of ECT
on pituitary hormone release, the term stress is used most often in the widest sense implying a range of physiological and psychological stimuli.

Rose (1984) has pointed out that there are considerable differences between individual animals and human beings in the response to a stress, that this response may be anticipatory, that is be at its greatest when the individual anticipates the event, but subside on exposure to the stimulus itself, and that a major determinant of the pattern of responses is the intensity of the stimulus.

Skrabinek et al. (1981) suggested that the endocrine effects of ECT are not specifically related to the induction of the seizure, but are the result of the physiological stimuli associated with anaesthesia and the fear of the procedure. The implication of this suggestion is that such endocrine effects are unlikely to be informative of the mode of action of ECT, nor associated with recovery. Reviewers agree that it is important to establish whether a biological consequence of ECT is associated either with the anti-depressant effect or the induction of seizure activity rather than, for example, the result of hypoxia during anaesthesia (Fink, 1979; Green & Nutt, 1987). The specific endocrine effects of the induction of cerebral seizure activity can be identified by the comparison of the effects of real ECT with simulated ECT.

**Methodological problems**

**Description of hormone response** Most studies of the endocrine effects of ECT use an insufficient number of blood sampling points before and after ECT. The release of pituitary hormones is pulsatile (Willoughby
et al., 1977; Stokes & Sikes, 1988) and the use of a single sample to estimate basal plasma hormone concentration may be unreliable (Stokes & Sikes, 1988). There is considerable variation in the timecourse of release among different pituitary hormones and yet some studies (Deakin et al., 1983; Robin et al., 1985) have used only one sampling point after ECT to measure the release of several hormones. Sufficient sampling points are required to identify when the peak plasma hormone concentration occurs and when the plasma hormone concentration has returned to the value before ECT. Once the timecourse of hormone release has been reliably described, a smaller number of sampling points may be used to estimate reliably the peak hormone plasma concentration (Swartz, 1985a).

Quantification of hormone release A variety of methods have been used to measure the effect of ECT on hormone release. Most studies have used the absolute increase in plasma hormone concentration either comparing a value immediately before ECT with a single sampling point after ECT (Deakin et al., 1983) or with the maximum value at two or three points after ECT (Haskett et al., 1985; Abrams & Swartz, 1985b). Robin et al. (1985) quantified hormone release by the ratio of the plasma hormone concentration 20 minutes after ECT to the concentration immediately before ECT. The expression of release as a percentage change over mean baseline hormone concentration (Skrabenek et al., 1981; Whalley et al., 1982) allows the effects of ECT on hormone release to be compared among different hormones. A more sophisticated method is to calculate the change in the area under the curve of mean plasma hormone concentration plotted against time which may reflect the change in availability of the hormone. This method has been used in
endocrine challenge tests (Loosen et al., 1982; Keks et al., 1987) but only once in an ECT study (Whalley et al., 1987) when the increase was calculated as percentage change to allow comparison among hormones. Although the area under the curve is likely to be closely correlated with these other measures of hormone release (Loosen et al., 1982), the effects of the choice of method in the quantification of hormone release on the results of ECT studies have not been assessed.

One rationale for the study of the effects of ECT on pituitary hormone release may be to test hypotheses concerning certain functions of the CNS during or after ECT. The measurement of hormone pituitary hormone concentrations in blood may fail to detect altered function in the CNS. A circadian rhythm in the CNS concentrations of both vasopressin (Reppert et al., 1981) and oxytocin (Artman et al., 1982) occurs in mammalian species and yet no circadian rhythm is apparent in plasma hormone concentrations. Vasopressin- and oxytocin- containing neurones are not confined to the hypothalamus and are widely distributed in the mammalian CNS (Buijs et al., 1985), and the relationship between the release of these hormones in CNS and systemic circulation has not been studied.

Measures of seizure activity Measures of seizure activity have usually relied on observation alone when the tonic contracture of muscles upon electrical stimulation may be confused with the tonic clonic movement of a generalized seizure (Fink & Johnson, 1982). Observation alone (even in a limb isolated from the effects of suxamethonium) often fails to detect unusually prolonged seizures and thus underestimates cerebral seizure activity (Greenburg, 1985). Occasionally seizure duration has been
measured by a single channel EEG tracing produced by the MECTA ECT
machine. Brumback (1983) found that single channel EEG recording from
bifrontal electrodes did not correlate with standard EEG tracings and
were particularly susceptible to muscle and eye movement artefacts.
Serious doubts about the inter-rater reliability of these measures have
been raised (Ries, 1985; Guze et al., 1989), although Warmflash et al.
(1987) have argued that training and discussion about the end-point
of the seizure can much increase the reliability of estimates. Single
channel EEG recording cannot estimate seizure generalization which may be
of importance not only in efficacy (Daniel, 1983), but in the endocrine
effects of ECT. Dana-Haeri et al. (1983) have shown that increases in
serum prolactin concentration in epileptic patients are greater after
generalized tonic clonic seizures than after focal or simple partial
seizures.

Other confounding factors Several factors which complicate the
interpretation of neuroendocrine tests of monoamine function have already
been mentioned above. Checkley (1980) suggested that psychotropic
drugs are probably the major confounding factor in studies of the
endocrine effects of ECT. Most patients may have received neuroleptic
and/or antidepressant drugs. When patients have been studied after
a period free of psychotropic drugs (except benzodiazepines), this period
has rarely been more than three weeks. Even the prescription of
benzodiazepine drugs may have confounding effects because of their potent
effects on gamma-aminobutyric receptors (Checkley, 1980) or because of
their anti-convulsant effects (Stromgren et al., 1980). The dilemma
is that to recruit depressed patients treated by ECT who could be nursed
satisfactorily in general admission wards without any psychotropic drugs
for several weeks would lead to a recruitment bias towards patients with less severe depressive illnesses who would be unrepresentative of contemporary patients treated by ECT.

**Conclusions on methodology** Most studies of the effects of ECT on pituitary hormone release have used too few blood sampling points to describe reliably the effects on hormone release; the use of a single sampling point to measure the release of several different hormones cannot be recommended. There is no general agreement about the quantification of hormone release after ECT and to what extent the results of studies depend on which method is chosen has not been assessed. It is important to establish whether a hormonal effect of ECT is related either to cerebral seizure activity itself or the antidepressant effects of the treatment. Most studies have used unreliable methods to measure cerebral seizure activity and these are unable to measure seizure generalization. In most studies of the antidepressant effect of ECT, no distinction is made between improvement and recovery, that is, whether or not a patient returns to a normal state of health. Definitions of recovery have been less demanding than the definition developed by the NIMH Collaborative Study on the Psychobiology of Depression (Keller et al. 1982). Future ECT studies should distinguish between improvement which can be measured at the end of a course of ECT and recovery, which should be confirmed up to eight weeks after treatment.
Anterior pituitary hormones

Prolactin

Researchers became interested in the effects of ECT on prolactin release for two reasons. First, the dominant role of the hypothalamus in the regulation of the release of prolactin is inhibitory (Leong et al., 1983) and the major inhibitory influence is the activity of the tuberoinfundibular dopaminergic system (Kling et al., 1987). Thus, prolactin release may be an indicator of the activity of certain dopamine-containing neurones during ECT. Secondly, generalized tonic clonic seizures, but not psychogenic seizures, lead to a substantial increase in serum prolactin concentration (Trimble, 1978). ECT leads to a several-fold increase in plasma prolactin concentration, reaching a peak between 10 and 15 minutes after treatment (Kling et al., 1987).

Effect of simulated ECT Prolactin release can be stimulated by a wide range of physiological and psychological stimuli in animals and human beings (Rose, 1984; Kling et al., 1987). Simulated ECT increases plasma prolactin concentration two-fold (Deakin et al., 1983), although this doubling did not reach statistical significance in the study of Arato et al. (1980) which used a smaller sample size.

Effect of electrical stimulation Direct electrical stimulation of the human brain has been reported to increase prolactin release only when limbic structures are involved (Kling et al., 1987). A single case study (Abrams & Swartz, 1935b) reported a substantial prolactin release
on three occasions where a depressed patient had received the electrical
stimulation in the absence of EEG or muscular evidence of a seizure.

ECT researchers have considered whether bilateral electrode
placement has a greater effect on prolactin release than unilateral
electrode placement, perhaps suggesting greater hypothalamic stimulation
(Abrams & Swartz, 1985b). Studies which have examined the effects of
electrode placement by making comparisons between patients treated by
either unilateral or bilateral ECT have reported no differences in
prolactin release (Balldin, 1982; Aperia et al., 1985). Studies which
have compared the effects of electrode placement within the same patients
have reported that the release of prolactin is slightly greater in
bilateral ECT for both modified sine wave (Papakostas et al., 1984;
Papakostas et al., 1986) and high energy wide-pulse stimulation (Swartz
& Abrams, 1984; Abrams & Swartz, 1985b).

Effects of seizure activity The release of prolactin is increased
after generalized tonic clonic seizures but not psychogenic seizures
(Trimble, 1978). The release of prolactin is a consistent finding in
cerebral seizure activity which involves limbic structures, but not focal
cerebral seizure activity outwith these areas (Dana-Haeri et al., 1983;
Sperling et al., 1986). Thus, in epileptic patients, seizure
generalization is an important influence on the release of prolactin.

Balldin (1982) reported that the increase in plasma prolactin
concentration after ECT correlated with the length of seizures estimated
by clinical observation, but did not reveal the strength of the
correlation. This finding was not confirmed when seizure length was
estimated by observation only (Aperia et al., 1985) nor by single channel EEG recording (Abrams & Swartz, 1985b). A more sophisticated study by Robin et al. (1985) used eight-channel EEG recording to measure cerebral seizure activity and found a correlation between the release of prolactin and EEG-measured seizure duration for high energy wave forms, but no correlation for low energy brief-pulse stimulation. Earlier studies give insufficient detail of the electrical stimulation to decide if high or low energy pulses were used, or, where such detail is given (Abrams & Swartz, 1985b), the effects of these two forms of electrical stimulation are not considered separately. Staton & Brumbeck (1985) argued that measures of cerebral seizure activity based on clinical observation or single channel EEG recording will never be sufficient to tease out the confounding effects of electrical energy, electrode placement, seizure length and seizure generalization on the endocrine effects of ECT.

Relation to recovery Abrams & Swartz (1985a) reported that in 16 depressed men who were free for two weeks of drugs which might affect plasma prolactin concentration, there was a positive correlation between the average increase in prolactin after the first four ECT and the total number of treatments ultimately prescribed, and a negative correlation with global improvement. Global improvement was rated once after six treatments, although up to 24 treatments were given. The authors concluded that a slow treatment response was correlated with a large increase in plasma prolactin concentration. An opposite finding was detected in a pilot study of nine depressed men and women who were not free of psychotropic drugs (Whalley et al., 1987). The release of prolactin after the first ECT (expressed as increase in area under the
time/concentration curve) correlated closely with the extent of improvement over a course of ECT measured as change in HRSD score. Two earlier studies had found no relationship between prolactin release and the extent of improvement over a course of ECT, but it is not stated whether Balldin (1982) studied patients suffering depressive illness and Deakin et al. (1983) studied patients after a fixed number of eight bilateral ECT.

In conclusion, prolactin release after ECT is the most thoroughly investigated endocrine effect of ECT. Although simulated ECT increases prolactin release, cerebral seizure activity is a much more potent stimulus. The generalization of cerebral seizure activity is an important determinant of the release of prolactin in epileptic patients, but the effects of seizure generalization have not been studied during ECT. Bilateral electrode placement releases more prolactin than unilateral placement, but the difference is small. Studies of the relationship between prolactin release and the likelihood of recovery from depressive illness have produced conflicting results. This may be because of a lack of consistency in the illnesses under study, methods of quantification of hormone release and clinical improvement, and the confounding effects of the intake of psychotropic drugs.

Adrenocorticotropin and cortisol

Interest in the release of cortisol as a potential biological measure of psychological stress led to the early study of the effects of ECT (Kling et al., 1987). Adrenocorticotropin (ACTH) peaks within five minutes of ECT (Allen et al., 1974; Aperia et al., 1984), although the peak release of cortisol is not observed until about 30 minutes after ECT.
(Aperia et al., 1984). The release of vasopressin after ECT may facilitate the release of ACTH (Widerlov et al., 1989).

Studies which have examined the effects of simulated ECT on cortisol and ACTH release have been inconclusive. Aperia et al. (1984) reported that simulated ECT had no effect on the release of ACTH or cortisol, but only six depressed patients were studied. In the largest study of the endocrine effects of simulated ECT, Deakin et al. (1983) reported that the release of cortisol was unaffected; however, the release of cortisol was estimated by a single blood sample 15 minutes after ECT, that is, before the peak occurs after real ECT.

Deakin et al. (1983) also reported that there was no relationship between the extent of the release of cortisol and clinical improvement from depression after ECT. Unfortunately, in the study of 33 depressed patients by Aperia et al. (1984), the authors do not discuss the relationship between the release of ACTH and cortisol and clinical recovery.

The release of ACTH and cortisol has been studied over a course of ECT in attempts to study changes associated with recovery. The results have been inconsistent. The release of ACTH and cortisol (Aperia et al., 1984) and cortisol (Weizman et al., 1987) have been found to be less after the sixth ECT than after the first ECT, but this effect on cortisol release has not been confirmed (Deakin et al., 1983; Haskett et al., 1985). Swartz & Chen (1985) studied the effects of ECT on cortisol release in 12 drug-free male depressed patients who had received 2 mg of dexamethasone nine hours before ECT; the release of cortisol was
much greater than usual and the release of cortisol was significantly less at the last ECT than at the first. They suggested that such a pattern of cortisol release was associated with clinical recovery. However, this conclusion seems unwarranted as of the two patients who did not show this pattern of cortisol release, one recovered and one did not.

In conclusion, ECT leads to a release of ACTH and cortisol, although factors which influence the extent of release are less studied than in the case of prolactin. A relationship between the extent of release of these hormones and clinical recovery after depressive illness has not been established.

Growth hormone (GH)

Data on the effects of ECT on the release of GH are inconsistent. Most studies which have used mixed diagnostic groups and made use of only a small number of blood sampling points have found no significant effects of ECT (see Haskett et al., 1985). However, a marked rise in GH has been reported about 30 min after ECT (Vigas et al., 1975; Skrabinek et al., 1981), and a significant fall has been reported during the 15 min after ECT (Deakin et al., 1983; Aperia et al., 1986) which is maximal one minute after treatment (Aperia et al., 1986).

Simulated ECT also leads to a fall in GH (Deakin et al., 1983) which is maximal within five min of treatment (Aperia et al., 1986). Most studies make no comment about the relationship between the release of GH and clinical outcome, but the two that did found no relationship (Deakin et al., 1983; Whalley et al., 1987).
In conclusion, recent studies stress the differences among patients in the effects of ECT on the release of GH which may not be surprising in view of the many factors which influence the release of GH. Simulated ECT leads to a fall in plasma GH concentration. This may be a direct effect of anaesthesia, or the release of GH may be anticipatory and subside on exposure to the feared stimulus itself (Rose, 1984). Electrical stimulation or cerebral seizure activity may lead to a rise in plasma GH concentration which compensates for the fall during anaesthesia. Certainly this is analogous to certain kinds of surgery where plasma GH concentration falls after pre-medication and only rises during the surgical procedure itself (Noel et al., 1972). The rise in plasma GH concentration may be in part a consequence of the tonic clonic movement because vigorous exercise and increased serum lactate concentration are potent stimuli of GH release; the study which found the greatest increase in plasma GH concentration (Vigas et al., 1975) was conducted in patients treated by unmodified ECT, that is, the electrical current was passed without pre-medication or muscle-blocking drugs. There is no evidence that the release of GH is related to recovery after ECT.

**Thyroid stimulating hormone (TSH)**

Early small studies usually in mixed diagnostic groups, found that ECT had no effect the release of TSH (see Dykes et al., 1987). Recent larger studies in depressed patients have provided conflicting results. Deakin et al. (1983) and Robin et al. (1985) reported that ECT had no effect on plasma TSH concentration, whereas Aperia et al. (1985) found
a significant rise in plasma TSH concentration 30 min after ECT. This discrepancy may be explained by the fact that the first two studies stopped blood-sampling 15 and 20 min after ECT. The findings of Dykes et al. (1987) are also relevant; they found that the release of TSH after ECT was closely correlated with the length of cerebral seizure activity measured by multi-channel EEG and only occurred consistently when seizures lasted at least 30 s. Data on the duration of seizure activity were not presented in the studies with negative findings, but Aperia et al. (1985) estimated seizure length by clinical inspection and the mean time was 32 seconds (range 20-70 seconds). Simulated ECT has no effect on the release of TSH (Aperia et al., 1985) and there is no relationship between the release of TSH after ECT and clinical improvement (Dykes et al., 1987).

Aperia et al. (1985) also found that the increase in serum TSH concentration was greater after the first ECT than after the sixth, suggesting to them an increase in post-synaptic dopamine receptor function, leading to the inhibition of TSH from the pituitary gland (dopamine agonists inhibit the release of TSH). Since the extent of the rise in serum TSH concentration after ECT is related to seizure duration, the observation that seizure duration usually decreases over the first six treatments of a course of ECT (Sackeim et al., 1987b) is an alternative explanation of this finding.

Beta-endorphin

At one time it was thought that endogenous opioids may be important in the mode of action of ECT (Emrich & Hollt, 1983). Consequently there was
interest in the effects of ECT on the release of beta-endorphin from the anterior pituitary. ECT produces a transient increase in plasma immunoreactive beta-endorphin concentrations (Alexopoulos et al., 1983; Misiaszek et al., 1984), although the time course of this increase has not been well described. (This might have been predicted as ACTH and beta-endorphin are synthesized as part of the same precursor molecule and then released together.) In a study of nine depressed patients, Weizman et al. (1987) found that, on average, the sixth ECT produced a two-fold greater effect on plasma beta-endorphin concentrations than the first ECT. However, Ghadirian et al. (1988) who also studied the release of beta-endorphin at the first and sixth ECTs in eight depressed patients, found that when data on individual patients were examined, the release of beta-endorphin was as likely to fall over a course of ECT as it was to rise. The effects of simulated ECT are unknown and there are no reports of any correlation between the extent of the release of beta-endorphin and clinical recovery.

Other hormones

Luteinizing hormone (LH) and follicle stimulating hormone (FSH) are also released from the anterior pituitary. The effects of ECT on the release of these hormones has been studied because ECT researchers were interested to learn whether the effects of ECT were selective for the release of certain hormones or whether there was an outpouring of all hormones from the anterior pituitary. The results of early studies are conflicting, but recent studies have found ECT has no effect on the release of LH (Robin et al., 1985) or a slight effect only at the first ECT (Whalley et al., 1987). There are spontaneous fluctuations
in the serum concentrations of these hormones, there may be differences between the sexes in the release of these hormones, and the release after LH may only occur in well generalized seizures (Dana-Haeri et al., 1983).

In conclusion, ECT does not have consistent effects on the release of LH and FSH.

Posterior pituitary hormones

Vasopressin

Gold et al. (1978) suggested that depressive illness may be associated with a deficiency of vasopressin and a later pilot study reported that high doses of a synthetic analogue of vasopressin improved mood in two of four depressed patients (Gold et al., 1979). A later study by Zohar et al. (1985) in 12 depressed patients whose illness had been resistant to tricyclic antidepressants found no anti-depressant effect of an alternative synthetic analogue of vasopressin.

Subsequent studies have been designed to investigate what, if any, changes occur in the release of vasopressin during depressive illness and upon recovery. However, it has been shown that ECT leads to a rapid and marked release of vasopressin which is maximal at two min (Raskind et al., 1979; Sorensen et al., 1982). The effect of simulated ECT on the release of vasopressin is unknown, but the anticipation of, and experience of, induction in general anaesthesia for surgery (Nussey et al., 1988) both lead to slight increases in the release of vasopressin.
The release of vasopressin is not related to seizure duration during ECT (measured on single-channel EEG) nor other factors that might influence release, for example, plasma osmolarity, plasma sodium concentration and plasma renin activity (Sorensen et al., 1982). Only one recent study (Widerlov et al., 1989) has commented on the possible relationship between vasopressin release after ECT and clinical recovery; there was no difference in the pattern of vasopressin response between 10 depressed patients who recovered after ECT and two patients (one of whom suffered from schizophrenia) who did not. There are no reports of any relationship between the release of vasopressin before a course of ECT and the likelihood of recovery.

**Oxytocin**

There are no reports of the effects of ECT on the release of oxytocin, although the effects of ECT on the release of the oxytocin-associated neurophysin are discussed below.

**Neurophysins**

The posterior pituitary peptide hormones oxytocin and vasopressin are synthesised as part of larger precursor molecules or pro-prohormones of which the neurophysins compose a large part (Ivell et al., 1983); these neurophysins are released at the same time and molar for molar with the parent hormones (see Robinson, 1975 and 1978, for reviews). The release of the vasopressin-associated neurophysin is increased by cigarette smoking and hence is known as the nicotine-stimulated neurophysin (NSN) and the release of the oxytocin-associated neurophysin...
is increased by the intake of oestrogen in human beings and hence is known as the oestrogen-stimulated neurophysin (ESN). The RIAs for the neurophysins require smaller samples of blood than those for vasopressin or oxytocin, and the half-life of the neurophysins in blood is twice that of the parent hormones.

Whalley et al. (1982) studied the immediate effects of ECT on the release of the neurophysins measured at one minute intervals for six minutes after treatment, and detected increases in release within one minute. The effects of simulated ECT on the release of the neurophysins is not known.

A follow-up study of the effects of general anaesthesia and surgery on the release of neurophysins in eight psychologically normal women undergoing elective cholecystectomy found the release of ESN was not affected, but there were some patients in whom mean plasma NSN concentration rose after surgery. These findings are the same as in a smaller study of four patients undergoing surgery (North et al., 1980). The effects of cerebral seizure activity on the release of neurophysins is not known.

Whalley et al. (1987) reported that the extent of increase in ESN after the first ECT (expressed as increase in area under the time/concentration curve) was closely correlated \( r = 0.7 \) with the improvement in HRSD score that occurred over a course of treatment in nine depressed patients. There was no relationship between the release of NSN and clinical improvement. This finding is of considerable
interest, and its replication was one of the first aims of the work in this thesis.

Conclusions

Careful assessment and recording of typical symptoms of depressive illness is the best available guide to the likelihood of recovery in depressed patients treated by ECT. Although the majority of patients will improve, about 15% will receive a course of ECT with little or no benefit. The use of existing predictive scales based on clinical features is no better than selection based on the typical features of depressive illness. There have, however, been major methodological limitations in previous clinical prediction studies, for example, the lack of a comparison group of placebo-treated depressed patients.

Clinical features alone may be insufficient to improve the predictive accuracy of selection of depressed patients for ECT. Consequently there have been many attempts to identify biological measures made before ECT which may be related to recovery. A biological measure related to recovery would also provide an important clue about the mode of action of ECT. As yet there is no such measure which is superior to clinical criteria in the selection of depressed patients for whom ECT would be an effective treatment.

Depressed patients have a wide range of physiological and behavioural reactions to ECT. Exposure to ECT itself may provide a better guide to prognosis in much the same way that a dynamic hormone
challenge test is more informative than the estimation of a random hormone concentration. The most important interaction between the patient and the ECT stimulus is that a self-limited tonic clonic seizure occurs, and this must be confirmed by the attendant psychiatrist. The present recommendation that the seizure must last at least 25 seconds is an arbitrary one. Although a generalized tonic clonic seizure is an essential component of successful ECT, this is not always sufficient. Further study is necessary to clarify the minimum requirements for an efficacious cerebral seizure. The relationship of initial seizure threshold and stimulus intensity to recovery and cognitive side-effects also merit further study.

The most widely investigated physiological consequence of ECT is the release of pituitary hormones. Attempts have been made to establish which of these hormonal effects are related to the psychological and physiological stimuli before and during anaesthesia, to cerebral seizure activity, or to the antidepressant effects of ECT. The interpretation of this work is difficult because of the unreliable methods used to measure hormone release and cerebral seizure activity and a lack of agreement in the timing and assessment of antidepressant effects. A pilot study suggested that the release of prolactin and ESN after the first ECT is closely correlated with the extent of eventual improvement in symptoms of depressive illness over a course of ECT. These findings are of considerable interest and require replication. This was the starting point for the work in this thesis.
The aims of the experiment were:

1. The detailed description of the effect of ECT on plasma concentrations of prolactin and ESN using several sampling points before and up to four hours after ECT.

2. Investigation of the relationship between the release of prolactin and ESN after the first ECT and recovery from depressive illness. Hormone release was expressed as absolute peak increase, percentage peak increase, and percentage increase in area under the curve. Distinction was made between the extent of improvement over a course of ECT and the state of recovery after ECT. The definition of recovery was similar to that used in the NIMH study on the psychobiology of depression (Keller et al., 1982).
Hypotheses

The following hypotheses were tested:

1. The increase in plasma prolactin concentration immediately after the first ECT of a course of treatment is correlated with the extent of improvement in symptoms of depressive illness over a course of treatment measured by the Hamilton Rating Scale for Depression (HRSD) and Brief Psychiatric Rating Scale (BPRS).

2. The increase in plasma ESN correlation immediately after the first ECT of a course of treatment is correlated with the extent of improvement in symptoms of depressive illness over a course of treatment measured as above.

Method

Ethics

The study protocol was approved in advance by the Psychiatry and Clinical Psychology Ethics of Research Sub-Committee of the Lothian Health Board.

Sample size

The closeness of the correlations between hormone release and clinical improvement found in the preliminary study (Whalley et al., 1987) was approximately $r = 0.7$. Power analysis (Cohen, 1977; table 3.3.5) showed
that with this closeness of correlation, a sample size of 16 patients would have a power of 90% to detect such a correlation with a two-tailed statistical significance of 0.05 using the Pearson product moment method.

Depressed patients

The sample consisted of 25 patients admitted to the Royal Edinburgh Hospital for inpatient treatment of depressive illness. The patients had not received ECT within six months, had no physical illness or symptoms suggestive of organic cerebral disease, and were able to give informed consent and comply with study procedures. There were 19 women (mean age 47.5 years, range 22-84) and six men (mean age 59.7 years, range 50-72) and all met Research Diagnostic Criteria (RDC, Spitzer et al., 1978) for Probable (N = 2) or Definite (N = 23) Major Depressive Disorder. Before ECT, only two of the patients were drug-free.

Clinical assessment

Illness severity was assessed by the HRSD (Hamilton, 1960) and the BPRS (Overall & Gorham, 1962). The BPRS was designed to measure symptoms and signs common in a number of psychiatric illnesses. Clinical ratings were obtained the day before the first ECT and seven to 10 days after the last, and were made without knowledge of the hormonal results.
Assessment of outcome

A course of ECT was deemed to be over when a patient went seven clear days without ECT. All patients received continuation doses of oral antidepressants after ECT. Immediate outcome was assessed as follows:

**Improvement** Improvement over the course of ECT was expressed as the absolute change (score before ECT minus score 7-10 days after ECT) on the two clinical rating scales.

**Good outcome** HRSD score less than 8 at 7-10 days after last ECT, and remained well with only continuation doses of oral antidepressants over those days.

**Poor outcome** HRSD score greater than 7 at 7-10 days after last ECT, or required increased or altered oral antidepressant drug because of depressive symptoms.

Outcome at two months was assessed by casenote review and was defined as follows:

**Good outcome** HRSD score less than 8 at 7-10 days after last ECT, discharged from hospital and remained well with no more than continuation antidepressant drug treatment.
Good outcome after more ECT  As above, but recurrence of depression within 10 days of last ECT and requiring more ECT but no additional antidepressant drug treatment.

Poor outcome  HRSD score greater than 7 at 7-10 days after last ECT, requiring increased or altered oral antidepressant drugs, or still in hospital or readmitted to hospital within two months.

All clinical assessments were made without knowledge of the hormonal results.

ECT

ECT was given between 0915 and 0945 h after an overnight fast. Anaesthesia was induced by thiopentone sodium followed by suxamethonium to produce muscle relaxation. No regular anaesthetic premedication was prescribed and no patient received atropine. The choice between unilateral and bilateral placement of electrodes was made by the referring psychiatrist. Bilateral ECT (11 patients) was given with electrodes in the bitemporal position and unilateral ECT (14 patients) with electrodes in the Lancaster position (temporoparietal). (The position of electrodes is illustrated in Fink, 1979.) The electrical stimulus at the first treatment was standard; a Neurotonic Therapy System ECT machine delivered 500 mA over 5 s in 2 ms pulses at a frequency of 100 Hz. The duration of a seizure was timed by the observation of clonic-tonic activity in an isolated forearm. A course of ECT consisted of an average of 6.9 treatments (range 2-12) as directed by
the responsible psychiatrist. When the interval between treatments exceeded seven days, the course of ECT was regarded as complete.

**Blood sampling**

An indwelling intravenous catheter was inserted about 90 min before ECT. Blood samples (5 ml) were taken 60 min, 30 min, and 2 min before treatment and after electrical stimulation, every 2.5 min to 15 min, then at 30 min, 1 h, 2 h, and 4 h. Blood samples were placed immediately into lithium-heparin-coated tubes and stored at 4°C. Plasma was separated by centrifugation at 4°C after collection of the last sample and stored at -40°C.

**Hormone assays**

Plasma hormone concentrations of ESN and prolactin were determined by means of the RIA kits from the National Institute of Arthritis, Diabetes, and Diseases of the Kidney (NIADDK). The reference preparation for ESN was that given to the NIADDK by Dr. A. Robinson, University of Pittsburgh. The sensitivities of the assays (90% B/Bo) were 80 pmol/l for ESN (100 µl sample) and 70mU/l for prolactin (50 µl sample). The mean coefficients of variation between and within assays of two or three quality controls for each assay were below 10%.

**Statistics**

The differences in clinical variables between outcome groups were assessed using Student’s group t-test for continuous variables, and chi
square and Fisher's exact probability test for discontinuous variables. The effects of ECT on plasma hormone concentrations were assessed by analysis of variance for repeated measures (Winer, 1971), using the Statistical Package for the Social Sciences Version X (SPSS-X, 1986).

Winer notes (page 281) that when the repeated observations are made on the same subjects (that is, correlated observations), heterogeneity of either the variances or covariances will result in a positive bias in the usual F test. Thus, a conservative correction of the F ratio was made as described by Winer. The differences in basal, peak and percentage peak hormone release between outcome groups was assessed using Student's group t test. The increase in the area under the curve of hormone concentration against time was calculated by the Trapezoidal Rule (Balfour & Beveridge, 1972). The hormone concentrations at consecutive sampling points after ECT were averaged and this average multiplied by the time between the samples. Areas between each pair of samples after ECT were summed to give an approximation of the total area under the curve after ECT. From this was subtracted the baseline area derived from the mean baseline concentration multiplied by the total time of sampling after ECT. The rise in area was expressed as a percentage increase of baseline area.

In the assessment of correlation between variables, the first step was to plot the data on a scattergram using the SPSS-X package. If the data were normally distributed, then the Pearson product moment correlation was used. If a significant correlation was obtained, the Bartlett-Box F test on SPSS was used to test for the homogeneity of variances and confirm the appropriateness of this parametric method of correlation. If the data were skewed, then the data were transformed to approximate to a normal distribution. If transformation was unsuccessful, then Spearman's rank method of correlation was used. Although the efficiency of the
Spearman method is only about 91% that of Pearson’s method (Siegel, 1956), the method does not assume that the measures are drawn from normal distributions, nor that the variance of the two measures is the same. All probabilities are expressed as two-tailed p values.

Results

Clinical details

Table IV shows the clinical and treatment details of the sample by immediate outcome. There were 16 patients who had a good outcome and nine patients who had a poor outcome 7-10 days after the last ECT. Good and bad outcome groups did not differ significantly in age, sex, RDC category, initial severity, or concomitant drug therapy. A greater proportion of the good outcome group received bilateral ECT (9 out of 16 patients versus 2 out of 9 patients in the poor outcome group), but this was not statistically significant (Fisher’s exact test, p = 0.11). There was only a slight trend for greater improvement in those patients treated by bilateral ECT and this was not statistically significant. The improvement in HRSD score was 16.0 ± 1.4 in those treated by unilateral ECT and 20.4 ± 1.8 in those treated by bilateral ECT.

Two patients who had a good immediate outcome relapsed and had a poor outcome at two months. They were still inpatients and had required drug therapy in addition to continuation antidepressant drug treatment (a phenothiazine drug in one case and lithium carbonate in the other). Two patients who had a poor outcome eight days after an initial series of ECT, received two additional ECTs and had a good outcome two months.
<table>
<thead>
<tr>
<th>Clinical details by outcome(^a) 7-10 days after last ECT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td>Good ((n = 16))</td>
</tr>
<tr>
<td>Poor ((n = 9))</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
</tr>
<tr>
<td>4M</td>
</tr>
<tr>
<td>2M</td>
</tr>
<tr>
<td><strong>Age (\pm) SEM</strong></td>
</tr>
<tr>
<td>56 (\pm) 3.8</td>
</tr>
<tr>
<td><strong>RDC category (^b)</strong></td>
</tr>
<tr>
<td>PMDD</td>
</tr>
<tr>
<td>PMDD-P</td>
</tr>
<tr>
<td>DMDD</td>
</tr>
<tr>
<td>DMDD-P</td>
</tr>
<tr>
<td>SAD</td>
</tr>
<tr>
<td><strong>Past history Manic Disorder</strong></td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td><strong>Initial HRSD (\pm) SEM</strong></td>
</tr>
<tr>
<td>24.1 (\pm) 1.5</td>
</tr>
<tr>
<td><strong>Initial BPRS (\pm) SEM</strong></td>
</tr>
<tr>
<td>19.3 (\pm) 7.2</td>
</tr>
<tr>
<td><strong>Antidepressant (AD) failure (^c)</strong></td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td><strong>Drug therapy at 1st ECT</strong></td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>Benzodiazepine (BZD)</td>
</tr>
<tr>
<td>Phenothiazine (PZ)</td>
</tr>
<tr>
<td>AD</td>
</tr>
<tr>
<td>AD + BZD</td>
</tr>
<tr>
<td>AD + PZ</td>
</tr>
<tr>
<td><strong>ECT: unilateral/bilateral</strong></td>
</tr>
<tr>
<td>7/9</td>
</tr>
<tr>
<td><strong>Number of ECT (\pm) SEM</strong></td>
</tr>
<tr>
<td>6.6 (\pm) 0.5</td>
</tr>
<tr>
<td><strong>Final HRSD (\pm) SEM</strong></td>
</tr>
<tr>
<td>3.0 (\pm) 0.4</td>
</tr>
<tr>
<td><strong>Final BPRS (\pm) SEM</strong></td>
</tr>
<tr>
<td>4.1 (\pm) 2.3</td>
</tr>
</tbody>
</table>

\(^a\) See Methods for categorization of outcome

\(^b\) RDC categories: PMDD = Probable Major Depressive Disorder;
PMDD-P = Probable Major Depressive Disorder, psychotic sub-type;
DMDD = Definite Major Depressive Disorder; DMDD-P = Definite Major Depressive Disorder, psychotic subtype; SAD = Schizoaffective Disorder, depressed type.

\(^c\) Current episode failed to respond to therapeutic dose of AD drug given for a minimum of four weeks

\(^d\) Significantly \((p < 0.001)\) greater than score in good outcome group.
after these additional treatments; they are included in the good outcome group.

Hormone release

In the total sample, the maximum mean plasma prolactin concentration occurred 12.5 min after ECT, and had not returned to baseline concentrations until 120 min after treatment. The maximum mean plasma ESN concentration occurred 2.5 min after ECT, and, like prolactin, did not return to baseline value until 120 min after treatment. Analysis of variance for repeated measures revealed significant effects of time in both conventional and conservative F tests. In the conservative F test of time for prolactin, $F = 24.0$, d.f. 1, 24, $p < 0.01$, and for ESN, $F = 33.2$, d.f. 1, 24, $p < 0.01$. There were no correlations between hormone release and the severity of depression nor the concomitant use of antidepressant drugs at the time of the first ECT.

Hormone release and clinical outcome

Figure 1 shows the mean plasma prolactin and ESN concentrations before and after the first ECT in the good (16 patients) and poor (nine patients) outcome groups at 7-10 days after the last ECT. There were no differences between the outcome groups in the mean baseline concentration of either hormone. When patients were categorized by outcome at two months, the 16 patients with a good outcome had a significantly lower mean baseline plasma ESN concentration than the nine patients with a poor outcome ($107 \pm 7$ pmol/l vs $144 \pm 14$ pmol/l, $p < 0.05$). This difference was confirmed when analysis was restricted to those patients.
Figure 1. Plasma hormone concentrations (mean ± SEM) before and after first ECT in the good (n = 16) and poor (n = 9) outcome groups at 7-10 days after the last ECT.

who had not taken phenothiazine drugs. The mean baseline plasma ESN concentration was significantly lower (p < 0.05) in the good outcome group (n = 12) compared to the poor outcome group (n = 6), that is, 101 ± 7 pmol/l vs 136 ± 14 pmol/l. The mean (+ SD) plasma ESN concentration is normally 88 ± 56 pmol/l in women and 80 ± 56 pmol/l in men (Robinson, 1975).
The pattern of the release of both hormones was similar in the outcome groups; although the absolute values at sampling points were consistently greater in the good outcome group. Analysis of variance for repeated measures revealed significant effects for a group-time interaction in conventional F tests for both hormones, but these effects were not significant in conservative F tests. (When the patients were categorized into good and poor outcome at two months, there was a significant group-time interaction for ESN in both conventional and conservative F tests. In the conservative F test of a group-time interaction, $F = 5.8$, d.f. 1, 24, $p < 0.05$. There was no significant time-group effect for prolactin.)

Table V shows the relations between the three measures of prolactin release after the first ECT and clinical outcome. The measurements were closely correlated with each other; the least close correlation was between the absolute peak increase and the percentage increase in area under the curve ($r = 0.81$, $p < 0.001$). The mean values of absolute peak increase and percentage increase in area under the curve in the good outcome group at 7-10 days were more than twice the values in the poor outcome group. When the patients were split by outcome at two months, there was a trend for a greater release of prolactin in the good outcome group but this trend was not statistically significant.

Table VI shows the relation between the three measures of ESN release after the first ECT and clinical outcome. The measurements of ESN release were closely correlated with each other; the least close correlation was between absolute peak increase and percentage increase in area under the curve ($r = 0.66$, $p < 0.01$). All three measurements of
### Table V

Relation between three measures (+ SEM) of prolactin release after first ECT and clinical outcome

<table>
<thead>
<tr>
<th>Measure</th>
<th>Outcome at 7-10 days</th>
<th>Outcome at 2 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Good (N = 16)</td>
<td>Poor (N = 9)</td>
</tr>
<tr>
<td>Absolute peak increase (IU/l)</td>
<td>1.69 ± 0.36&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.67 ± 0.21</td>
</tr>
<tr>
<td>Percentage peak increase</td>
<td>401 ± 130</td>
<td>228 ± 101</td>
</tr>
<tr>
<td>Percentage increase in area under concentration/time curve</td>
<td>277 ± 70&lt;sup&gt;b&lt;/sup&gt;</td>
<td>105 ± 36</td>
</tr>
</tbody>
</table>

<sup>a</sup> See Methods for categorization of clinical outcome

<sup>b</sup> Significantly (p < 0.05) greater than value in poor outcome group

### Table VI

Relation between three measures (+ SEM) of ESN release after first ECT and clinical outcome

<table>
<thead>
<tr>
<th>Measure</th>
<th>Outcome at 7-10 days</th>
<th>Outcome at 2 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Good (N = 16)</td>
<td>Poor (N = 9)</td>
</tr>
<tr>
<td>Absolute peak increase (pmol/l)</td>
<td>124 ± 20&lt;sup&gt;b&lt;/sup&gt;</td>
<td>70 ± 12</td>
</tr>
<tr>
<td>Percentage peak increase</td>
<td>122 ± 20&lt;sup&gt;b&lt;/sup&gt;</td>
<td>58 ± 12</td>
</tr>
<tr>
<td>Percentage increase in area under concentration/time curve</td>
<td>53 ± 9&lt;sup&gt;c&lt;/sup&gt;</td>
<td>21 ± 5</td>
</tr>
</tbody>
</table>

<sup>a</sup> See Methods for categorization of clinical outcome

<sup>b</sup> Significantly (p < 0.05) greater than value in poor outcome group

<sup>c</sup> Significantly (p < 0.01) greater than value in poor outcome group

<sup>d</sup> Significantly (p < 0.001) greater than value in poor outcome group
mean ESN release were greater in the good outcome groups than in the poor outcome groups at 7-10 days and two months. The difference in mean ESN release between the outcome groups was greater when outcome was assessed at two months after the last ECT.

When measurements of ESN release for individual patients were plotted by outcome groups, the overlap between the outcome groups was least when ESN release was expressed as the percentage peak increase. Figure 2 shows the relation between percentage peak increase in plasma ESN concentration and clinical outcome. All nine patients in whom percentage peak plasma ESN concentration increased by more than 100% were in the good outcome group. If a 63% rise in ESN was used to classify all subjects, three (12%) were misclassified by outcome group at two months. This gives a predictive accuracy of 88%.

Hormone release and clinical improvement

Clinical improvement was measured by change scores on the clinical rating scales. The change scores on the HRSD were skewed towards the upper end of the range and it was not possible to transform the data to approximate a normal distribution. For consistency, Spearman's rank method was used to assess the associations between hormone release and change on both clinical rating scales.
Figure 2. Relationship between percentage peak ESN release after first treatment of a course of ECT and clinical outcome 7-10 days and two months after last ECT.
Table VII shows that the increase in plasma ESN concentration after the first ECT correlated with clinical improvement on the HRSD but not the BPRS. This suggests that ESN release is more closely correlated with improvement in symptoms typical of depressive illness rather than global illness severity rated by the BPRS. The closest correlation between ESN release and improvement in HRSD score was when hormone release was quantified as percentage peak increase and the data are shown in Figure 3. There were no significant correlations between any of the measures of prolactin release and clinical improvement on either rating scale.

**TABLE VII**

<table>
<thead>
<tr>
<th>Measure</th>
<th>HRSD Prolactin</th>
<th>ESN</th>
<th>BPRS Prolactin</th>
<th>ESN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute peak increase</td>
<td>0.13</td>
<td>0.36&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-0.01</td>
<td>0.18</td>
</tr>
<tr>
<td>Percentage peak increase</td>
<td>0.28</td>
<td>0.46&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-0.09</td>
<td>0.12</td>
</tr>
<tr>
<td>Percentage increase area</td>
<td>0.20</td>
<td>0.42&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-0.18</td>
<td>-0.15</td>
</tr>
</tbody>
</table>

under concentration/time curve

<sup>a</sup> Clinical improvement expressed as change in score on rating scale between day before first ECT and seven to 10 days after last ECT

<sup>b</sup> p < 0.05

The above findings were confirmed when the assessment of the relationships between the release of hormones and clinical improvement was restricted to those patients who had not received phenothiazine drugs (n = 18). The percentage peak increase in plasma ESN concentration was correlated with improvement in HRSD score (ρ = 0.49, p < 0.05), but not
Figure 3. Relation between percentage peak increase in plasma ESN concentration after the first ECT and improvement in HRSD score over a course of treatment.
with change in BPRS score (rho = 0.11). There were no significant correlations between any of the measures of the increase in plasma prolactin concentration and clinical improvement. The correlations between percentage peak increase in plasma prolactin concentration and improvement in HRSD and BPRS scores were -0.14 and 0.20 respectively.

Seizure activity

There was no significant difference in seizure length at the first ECT between the outcome groups defined 7-10 days after the last ECT. Seizure length was $34.4 \pm 2.1$ s in the good outcome group and $32.2 \pm 3.0$ s in the poor outcome group.

There were no significant correlations between any of the measures of hormone release and seizure activity estimated by clinical observation of an isolated forearm. The correlations (Pearson's method) between seizure length and percentage peak hormone increase was $r = 0.19$ for prolactin, and $r = 0.16$ for ESN.

There were no significant differences in any of the measures of hormone release between unilateral and bilateral electrode placement. The percentage peak prolactin increase was $415 \pm 75\%$ in those patients treated by unilateral ECT ($n = 14$), and $260 \pm 85\%$ in those treated by bilateral ECT ($n = 11$). The percentage peak ESN release was $99 \pm 21\%$ in those treated with unilateral ECT and $106 \pm 22\%$ in those treated by bilateral ECT.
Hypotheses

1. There was no support for the hypothesis that the extent of the increase in plasma prolactin concentration after the first ECT correlates with the extent of eventual improvement in symptoms of depressive illness after a course of ECT.

2. The findings support the hypothesis that the extent of the increase in plasma ESN concentration immediately after the first ECT correlates with the extent of eventual improvement from depressive illness measured by the HRSD, but not the BPRS.

Other findings

Baseline ESN concentration An unexpected finding (in these 25 unipolar and bipolar depressed patients) was that the baseline plasma ESN concentration in those patients with a good outcome at two months was about two-thirds that of the patients with a poor outcome at two months. There are no data on the effects of depressive illness on plasma ESN concentrations, but Legros et al. (1983) have reported normal concentrations of the oxytocin-associated neurophysin in the CSF of unipolar depressed patients when compared to a control group of neurological patients. There was no difference in the plasma ESN concentration between patients with a good and poor outcome when outcome was assessed 7-10 days after ECT. This finding may have arisen by chance and requires replication.
Measures of hormone release As might have been predicted by the work of Loosen et al. (1982), the measurements of hormone release using the three different methods were closely correlated. Moreover, both the positive and negative findings for each hormone were consistent among the three measures of hormone release. In part, this may be because the frequent sampling times allowed for the accurate identification of the maximum or peak plasma hormone concentration. The finding of a correlation between ESN release and clinical improvement is not dependent on the method used to measure hormone release.

Potential prediction of recovery When patients were classified by outcome at seven to 10 days and two months after the last ECT, the increase in plasma ESN concentration was consistently greater in the good outcome groups for each measure of hormone release. This difference was most marked at two months and when ESN release was measured as percentage peak increase. There was little overlap between the outcome groups in ESN release, and had a 63% increase been used to classify all subjects into those who would recover and those who would not, then the predictive accuracy of this test would have been 88%. This finding suggests that the release of ESN merits further assessment as a putative predictor of clinical recovery after ECT.

The increase in plasma prolactin concentration tended to be greater in those patients with a good outcome seven to 10 days after the last ECT than patients with a poor outcome, although this difference was only statistically significant for two of the measures of hormone release. This is compatible with the finding that there is no significant
correlation between the increase in plasma prolactin concentration and the eventual improvement in symptoms of depressive illness. There were no significant differences in the increase in plasma prolactin concentration between outcome groups at two months after the last ECT. Unlike the data for ESN, there was considerable overlap in the increase in plasma prolactin concentration between outcome groups.

Potential sources of error

Sample The vast majority of patients met RDC for Definite Major Depressive Disorder, which is representative of the type of patients treated today by ECT (Rich et al., 1984). It is likely that the sample did not include the most severely ill or behaviourally disturbed patients who were either not able to give consent or comply with the study.

Measurement of hormone release Swartz (1985a) pointed out that measures of hormone release which ignore the rate of elimination of hormone from the blood cannot measure the total amount of hormone released from the pituitary. Swartz proposed a model of hormone release and elimination expressed as a kinetic equation for which the total amount of prolactin released can be calculated. McGuire et al. (1989) re-examined the data for prolactin and ESN release in the first nine patients in the present experiment and found that it was possible to solve the kinetic equation with unique coefficients in only half of the data sets. The authors concluded that the model proposed by Swartz did not lead to reliable measures of prolactin and ESN release after ECT (see attached publication).
Few studies of the effects of ECT on hormone release have supplied information about the reliability of the RIAs, but the reliability of the RIAs in the present study is similar to that reported elsewhere (Balldin, 1982; Abrams & Swartz, 1985b; Turner et al., 1987). All plasma samples from the same patient were analyzed in the same assay to minimize the effects of inter-batch error.

The RIA for ESN is a valid measure of the release of oxytocin; the plasma ESN concentration is closely correlated \((r > 0.8)\) with the plasma oxytocin concentration (Amico et al., 1981).

**Hormone release and phenothiazines** Swartz (1986) has argued that phenothiazine drugs may have confounding effects on the relationship between the release of pituitary hormones and clinical outcome. The intake of phenothiazine drugs increases plasma prolactin concentration; the strength of the effect varies several-fold between individuals but tends to be greater in women (Ohman & Axelsson, 1980). The findings of the present experiment did not depend on the intake of phenothiazine drugs. The significant correlation between the increase in plasma ESN concentration and improvement in depression was confirmed when the analysis was restricted to those patients who had not received phenothiazine drugs and no significant correlation was found between the increase in plasma prolactin concentration and improvement in these phenothiazine-free patients.
Other confounding effects Age, sex and reproductive status influence the release of pituitary hormones (Checkley, 1980). An increase in plasma oestrogen concentration is known to stimulate ESN release (Amico et al., 1981). A re-analysis of the association between percentage peak increase in plasma ESN concentration and improvement in HRSD score showed a closer correlation in men (rho = 0.56) than in women (rho = 0.38). This trend would support the supposition that the correlation is less close in the presence of higher concentrations of circulating oestrogen, although this requires confirmation in a larger sample.

Release of hormones from periphery The rationale for the measurement of plasma pituitary hormone concentrations is that these substances are released from the pituitary and reflect activity in the CNS. Prolactin is synthesized and secreted only by acidophilic cells in the anterior pituitary called lactotropes (Leong et al., 1983) and thus the total concentration of prolactin in the plasma must originate there. Although the greatest concentration of ESN is synthesized and released from the posterior pituitary, ESN has been identified by RIA in peripheral organs such as the ovary, testis, adrenal medulla and thymus (Geenen et al., 1986). The physiological significance of the identification of ESN in these sites is unknown, and it is not known if ESN can be synthesized and released from these peripheral organs.

Clinical assessment The HRSD is a valid instrument to measure the severity of depressive illness, in that HRSD total scores are strongly related to other clinical judgements concerning the severity of depression (Hedlund & Vieweg, 1979). Changes in HRSD score are also
observed to reflect clinically observed changes in depressed patients receiving antidepressant treatment (Hedlund & Vieweg, 1979). All the patients were assessed by the one rater which excludes the possibility of error because of differences between raters. No data are available on the reliability of the rater in the present study, but inter-rater reliability measured by correlation is usually about 0.9 (Hedlund & Vieweg, 1979).

High inter-rater reliability has been shown for the individual items of the 16-item BPRS and the scale has been shown to be sensitive to change (Overall & Gorham, 1962). No validity data are available for the BPRS.

Classification by clinical outcome None of the patients in the sample was under the direct care of the researcher. The number of ECT given to each patient was decided by the responsible psychiatrist. It is not possible to predict how many ECT will be required by an individual patient (ECT Sub-Committee of the Royal College of Psychiatrists, 1989) and it may be that some patients who were in the poor outcome group immediately after ECT would have fared better with further ECT. Indeed, this did happen with two patients. Although all patients received continuation antidepressant treatment after ECT, this was supervised by the ward staff and there was no check of compliance apart from asking each patient if they took the drugs. In such a design, it is possible that a patient who had the potential to recover after ECT relapsed because of a lack of compliance with antidepressant drug treatment, although there was no patient in the present experiment who fitted this pattern. In short, one cause of relapse is that patients do not accept the treatment the doctor offers.
Seizure activity. The limitations of the measurement of seizure activity by clinical observation alone have already been discussed in the review of the literature. The findings of the present experiment that there was no relationship between the release of ESN and seizure activity must be open to question and will be addressed in the next experiment.

Spurious correlations. Correlations are expressions of the degree of association between two variables (Halperin, 1986). Spurious correlations may arise when the Pearson product moment correlation method is used as this is a measure of linear association between two variables which are assumed to have a normal distribution (Halperin, 1986). This problem does not arise in the present experiment because the method used to assess the association between clinical improvement and hormone release was Spearman's rank method which does not require that the data are normally distributed. All methods of correlation, however, are influenced by the range of the variables (Halperin, 1986). This is one important reason why findings based on correlation require replication in a further sample.

Explanation of findings

The neurotransmitter mechanisms which underlie the release of pituitary hormones will vary according to the stimulus involved; consequently the best models to study these mechanisms are in ECT itself or ECS in animals. Most of the work on the biochemistry of seizures has been carried out in rodents (Green, 1987) and it is not clear to what extent these results can be extrapolated to human beings.
Prolactin There is debate about the mechanism of release of prolactin after a single ECT. Deakin et al. (1983) noted that prolactin release is powerfully inhibited by the tuberoinfundibular dopaminergic system and concluded that ECT-induced release of prolactin indicated an acute antidopaminergic effect of ECT. The authors suggested that an endogenous opioid may be involved. Whalley et al. (1987) suggested that a more important factor in prolactin release was the increase of a prolactin releasing factor such as TRH or vasoactive intestinal peptide; moreover, they argued that the neurotransmitter 5-HT was the most likely of central neurotransmitters to be involved in prolactin release. Subsequently it was shown that naloxone (an antagonist at mu, kappa and sigma opioid receptors) does not alter prolactin release after ECT (Turner et al., 1997; Sparling et al., 1989). This suggests that endogenous opioids are not involved in the release of prolactin after ECT. The involvement of 5-HT in the mechanisms of prolactin release has been investigated by the administration of the non-selective 5-HT receptor antagonist, methysergide, which has been shown to reduce the release of prolactin after ECT (Papakostas et al., 1988) whereas ketanserin, which antagonizes 5-HT₂ receptors preferentially, has no effect on prolactin release (Zis et al., 1989). Papakostas et al. (1988) pointed out that methysergide is an ergot compound and thus also has dopaminergic properties; stimulation of the tuberoinfundibular dopaminergic system might also be a mechanism of reduced prolactin release; however, ketanserin binds with roughly the same affinity to dopamine receptors without diminishing prolactin release. On balance, these findings support a role for the 5-HT₁ receptor in ECT-induced prolactin release. A recent study has also shown that electrical
stimulation of the paraventricular area in rats increases the release of TRH from the hypothalamus (Rondeel et al.; 1989) and ECS in rats increases the content of TRH in the forebrain (Kubek et al.; 1985). This evidence is not conclusive, but would support the role of TRH as a prolactin-releasing factor during ECT.

Although the release of prolactin is increased by spontaneous and electrically-induced seizures, the release of prolactin is not consistently related to either improvement or the likelihood of recovery from depressive illness after ECT. This is probably because of the great variability of prolactin release among individuals which depends on age, sex, reproductive status and the intake of psychotropic drugs. Moreover, other psychological and/or physiological stimuli that occur before and during anaesthesia for ECT lead to prolactin release because simulated ECT leads to a two-fold increase in plasma prolactin concentration; thus, factors other than the therapeutic ingredient of ECT influence prolactin release. This is probably the main reason that prolactin release does not predict outcome accurately.

Much of what is known of the control of the release of ESN is derived from studies of the release of oxytocin in suckling rats (Lincoln & Paisley, 1982; Poulain & Wakerley, 1982; Lincoln & Russell, 1985). The major determinant of the release of oxytocin and its associated neurophysin is the frequency of discharge of oxytocin-containting neurones in the paraventricular and supraoptic nuclei. Indeed, this was the first physiological situation in which there was a precise correlation between electrical activity and hormone secretion. Endogenous opioids and other neurotransmitters (to be enumerated in the next chapter) may also
contribute to the regulation of oxytocin release, but study of these mechanisms has usually involved systemic or intra-cerebroventricular administration and the physiological relevance of many of these studies is unclear (Poulain & Wakerley, 1982). Stronger evidence exists that oxytocin release is inhibited by opiates and opioid peptides and that naloxone antagonizes these inhibitory responses (Lincoln & Russell, 1985). The simplest explanation of ESN release after ECT is that it is the result of electrical activity or seizure activity in the magnocellular neurones which release oxytocin and ESN. The rate of release of oxytocin is in proportion to the number of action potentials entering the posterior pituitary (Lincoln & Paisley, 1982). In the rat, electrical stimulation of the posterior pituitary in 2 ms pulses at 50 Hz releases 100 times as much oxytocin as stimulation at 1-5 Hz. (The electrical stimulation in the present experiment consisted of 2 ms pulses at a frequency of 100 Hz.)

The effect of simulated ECT on the release of ESN is not known, but anaesthesia alone has no effect (North et al., 1980; Whalley et al., 1987). Thus the release of ESN may be more specific to stimuli occurring during ECT than, say, in the case of prolactin. The release of ESN may be related to improvement and outcome because patients who release most ESN have the most intense or the most widely generalized seizures (Daniel, 1983), or they are more likely to have received an electrical stimulus which is considerably in excess of the seizure threshold (Devanand & Sackeim, 1988). The extent of the contribution of the intensity of electrical stimulation to the antidepressant effect of ECT is still uncertain and, thus, the more cautious explanation is that ESN
release is a correlate of either seizure intensity or seizure generalization.

This hypothesis is not supported by the non-significant trend for unilateral ECT to lead to a greater release of ESN than bilateral ECT; however, studies which have examined the effects of electrode placement on hormone release by comparing results between patient groups treated by either unilateral or bilateral ECT have failed to detect findings reported when comparisons are made within the same patients (see Review of the Literature).

A more speculative possibility is that ESN, oxytocin or a substance released at the same time as ESN, directly contributes to the antidepressant effect of ECT. This speculation will be considered later.

Future study

A further study will be necessary to test the hypothesis derived from the present findings that the release of the oxytocin-associated neurophysin after the first ECT is a correlate of the intensity or generalization of cerebral seizure activity. A reliable method to measure cerebral seizure activity will be required to test this hypothesis.

A replication study in a new sample of patients can assess further the clinical utility of the relationship between oxytocin-associated neurophysin release and recovery in the prediction of ECT outcome. The confirmation of the correlation between neurophysin release and clinical
improvement will in itself be an endorsement of the reliability of the methods used.

RIA for neurophysins

RIAs for the neurophysins have been developed separately in laboratories in North America and Europe. There is at present no international standard and it is possible that results obtained in one laboratory are not directly comparable with another. The RIA for measuring immunoreactive neurophysins (IRN) was first described by Legros (Legros et al., 1969) who later established a method to detect the vasopressin-associated neurophysin which migrates to the anode in electrophoresis and is thus named human neurophysin-I (hNPI). Working separately, a group in Pittsburg (Robinson, 1975) followed with methods for a neurophysin which increased in plasma in response to cigarette smoking (NSN, which is equivalent to the vasopressin-associated neurophysin) and a neurophysin which increased in plasma in response to oestrogen (ESN, which is equivalent to the oxytocin-associated neurophysin). IRN is equivalent to the total amount of oxytocin- and vasopressin-associated neurophysins in peripheral blood (Legros, 1975). The first experiment used RIA materials generously donated to the pituitary hormone programme of NIADDK by Dr Robinson. In the next experiment, the measurement of serum neurophysin concentrations will be made by Dr Legros at the University of Liege using his own RIA. Using this RIA, Legros et al. (1983) showed that there are differences between unipolar and bipolar depressed patients in the release of the neurophysins, thus the next experiment will be restricted to unipolar depressed patients. Hormone release will be expressed as percentage
peak increase above mean baseline. This expression gave the closest correlation between ESN release and clinical outcome.

Cerebral seizure activity The limitations of the cuff technique and single-channel EEG recording as measurements of cerebral seizure activity have already been discussed in detail above. The cuff technique underestimates cerebral seizure activity and single channel EEG recording is prone to artefact. Neither method can estimate seizure generalization which may be an important influence on hormone release after ECT. In the next experiment, the duration of cerebral seizure activity will be measured by six-channel EEG recording which allows better identification of muscle artefact and more reliable measurement of the length of spike-wave activity, which is "the signature of a seizure" (Martin, 1985). Moreover, it is the spatial distribution of the spike-wave activity that distinguishes focal seizures from those that become generalized.
EXPERIMENT TWO: RECOVERY, SEIZURE ACTIVITY AND NEUROPHYSIN RELEASE AFTER ECT

Aims

The aims of the experiment were:

1. The confirmation that ECT leads to a rapid increase in serum concentrations of the vasopressin- and oxytocin-associated neurophysins using the alternative RIA for the measurement of neurophysins (Legros et al., 1969; Legros, 1975).

2. The confirmation that the release of the oxytocin-associated neurophysin after the first ECT is correlated with the extent of improvement in the symptoms of depressive illness over the course of ECT. Measurement of improvement included assessment by the Montgomery and Asberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979) which is a more recent depression rating scale specifically designed to be sensitive to change during treatment for depressive illness.

3. The investigation of the relationship between the release of the neurophysins and seizure activity using simultaneous multichannel EEG recording of ECT-induced cerebral seizure activity.
Hypotheses

The following hypotheses were tested:

1. ECT leads to a rapid increase in the serum concentrations of oxytocin-associated neurophysin (hNpII) and vasopressin-associated neurophysin (hNpI) as measured by the RIA developed by Legros.

2. The percentage peak increase in serum hNpII concentration after the first ECT of a course of treatment is correlated with the extent of improvement from unipolar depressive illness, measured by change in HRSD and MADRS scores.

3. The release of hNpII is the result of cerebral seizure activity and thus is correlated with the duration of spike-wave activity and/or total cerebral seizure activity measured by simultaneous EEG recording.

Method

Ethics

The study protocol was approved in advance by the Psychiatry and Clinical Psychology Ethics of Research Sub-Committee of the Lothian Health Board.
Depressed patients

The sample consisted of 19 patients admitted to the Royal Edinburgh Hospital for inpatient treatment of unipolar depressive illness and referred routinely for ECT. Patients with a past history of mania or hypomania were not included. The patients had not received ECT within six months, had no physical illness or symptoms suggestive of organic cerebral disease and were able to give informed consent and comply with study procedures. None of the patients was hypertensive or obese. There were 16 women (mean age 46.5 ± 4.3 years, range 28-78) and three men (mean age 54.6 years, range 56-72), and all met RDC (Spitzer et al., 1978) for Probable (n = 1) or Definite (n = 18) Major Depressive Disorder. All of the patients were taking psychotropic drugs before ECT.

Clinical assessment

The BPRS rating scale was replaced by the MADRS, otherwise all methods of clinical assessment and outcome were the same as in Experiment One.

ECT

Bilateral ECT (10 patients) and unilateral ECT (nine patients) were prescribed by the supervising clinician. Unilateral ECT was given with electrodes in D'Elia's position (temporoparietal) to avoid contact with EEG scalp electrodes. (Position of electrodes is illustrated in Fink, 1979.) Electrical stimulus at the first treatment was standard: an Ectron CCX Series 3 ECT machine delivered 850 mA over five s in 1.5 ms pulses at
a frequency of 45 Hz.

**EEG monitoring**

About 15 min before the first ECT, the patient lay down on a trolley and EEG electrodes were attached to the scalp by collodion. Seizure activity was measured on six channels (pF1-Cz, pF2-Cz, F3-Cz, F4-Cz, C3-Cz, C4-Cz) of a portable EEG machine made by Specialised Laboratory Equipment Ltd (model LOOP). The University Department of Medical Engineering and Physics designed an electronic relay which when triggered by the ECT stimulus isolated the EEG machine for the duration of the stimulus. EEG tracings could be obtained within two to three seconds of the treatment stimulus and were continued until the patient was moved to the recovery suite.

**Measures of seizure activity**

Three measures of seizure activity were made using the six-channel EEG record. Total seizure length was the time from the end of electrical stimulation to the end of any paroxysmal cerebral seizure activity. Spike-wave activity was timed from the end of electrical stimulation to the end of bilateral spike-wave activity and also to the last spike wave on any channel. The measures of seizure activity were made by an independent EEG rater (IO), who had no knowledge of the patient's clinical status or of the hormone results.
Blood sampling

Cigarette smoking is a potent stimulus for the release of the vasopressin-associated neurophysin in some people (Robinson, 1978; North et al., 1980). Thus patients were not allowed to smoke between cannulation and the last blood sample. In view of this, and since the maximum release of the neurophysins was predicted to occur within a few minutes of ECT, the length of blood sampling was reduced to 60 min after ECT. Blood sampling for longer than 60 min after ECT may allow other factors such as the ingestion of psychotropic drugs to influence plasma hormone concentrations once the patients have resumed normal daytime activities on the admission wards.

An indwelling intravenous catheter was inserted about 60 min before ECT. Blood samples (5 ml) were taken 30 min, 15 min and one min before treatment, and after electrical stimulation at 2.5, 5, 7.5, 10, 12.5, 15, 30 and 60 min. Blood samples were placed immediately in plain tubes and stored at $4^\circ$C. Serum was separated by centrifugation and samples stored at $-20^\circ$C.

Hormone assays

Serum hormone concentrations were determined in the Neuroendocrinology Section at the University of Liege. IRN was measured using the original RIA described previously (Legros et al., 1969); vasopressin-neurophysin (hNP1) was assayed using a new RIA. hNP1 was used as standard and labelled. The labelling of hNP1 was realized as for the IRN RIA, the specific activity being $225 \pm 25 \mu\text{c}/\mu\text{g}$. Anti-hNP1 antiserum was used
at the initial dilution of 1/10,000. Separation of free from bound hormones was achieved by double antibody techniques. At this dilution, +30% of the tracer (+9,000 cpm) was bound; the limit of detection being 0.02 ng/tube, and the sensitivity (50% inhibition binding) being 0.2 ng/tube. The volume of known or unknown samples was usually 100 μl.

Cross reaction of oxytocin-neurophysin (hNpII) was detectable at 0.01 level; no cross reactivity was detected using synthetic nonapeptide (oxytocin or vasopressin) or purified extracted human antehypophyseal hormone. Intra-assay variability was 6.5% and inter-assay variability was 10.7%; all the samples of one individual were assayed in the same run.

Statistics

See Experiment One.

Results

Clinical details

There were seven patients who had a good outcome and 12 patients who had a poor outcome 7-10 days after the last ECT. One patient who had a good immediate outcome relapsed and had a poor outcome at two months. Table VIII shows the clinical and treatment details of the sample by outcome at two months after the last ECT.

There were no significant differences between the two groups before ECT in age, sex, RDC category, severity of depression or drug treatment. A greater proportion of the good outcome group received bilateral ECT (four out of six patients versus six out of 13 patients) but this was not
TABLE VIII
Clinical details by outcomea two months after last ECT

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Good (n = 6)</th>
<th>Poor (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>1M</td>
<td>2M</td>
</tr>
<tr>
<td></td>
<td>5F</td>
<td>11F</td>
</tr>
<tr>
<td>Age ± SEM</td>
<td>54 ± 5.0</td>
<td>48 ± 4.8</td>
</tr>
<tr>
<td>RDC category b:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMDD</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>DMDD</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>DMDD-P</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Initial HRSD ± SEM</td>
<td>21.3 ± 2.3</td>
<td>23.9 ± 1.5</td>
</tr>
<tr>
<td>Initial MADRS ± SEM</td>
<td>30.8 ± 3.3</td>
<td>35.6 ± 1.8</td>
</tr>
<tr>
<td>Failed antidepressant (AD) drug therapy</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Drug therapy at 1st ECT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepine (BZD)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Phenothiazine (PZ)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>AD</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>AD + BZD</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>AD + PZ</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>ECT: unilateral/bilateral</td>
<td>2/4</td>
<td>7/6</td>
</tr>
<tr>
<td>Number of ECT ± SEM</td>
<td>7.3 ± 1.0</td>
<td>7.1 ± 0.6</td>
</tr>
<tr>
<td>Final HRSD ± SEM</td>
<td>3.0 ± 1.0</td>
<td>14.0 ± 1.9d</td>
</tr>
<tr>
<td>Final MADRS ± SEM</td>
<td>5.0 ± 2.3</td>
<td>17.6 ± 3.3e</td>
</tr>
</tbody>
</table>

a See Methods for categorization of clinical outcome.

b RDC categories: PMDD = Probable Major Depressive Disorder; DMDD = Definite Major Depressive Disorder; DMDD-P = Definite Major Depressive Disorder, psychotic subtype.

c Current episode failed to respond to therapeutic dose of AD drug given for a minimum of four weeks.

d Significantly (p < 0.01) greater than score in good outcome group.

e Significantly (p < 0.05) greater than score in good outcome group.
Figure 4. Serum neurophysin concentrations (mean ± SEM) before and after first treatment of a course of ECT by clinical outcome two months after last ECT. * Concentration in the poor outcome group (N = 13) significantly (p < 0.05) greater than concentration in the good outcome group (N = 6).
statistically significant (Fisher's exact test, \( p = 0.63 \)). There was a trend for the improvement in HRSD score to be greater in those patients treated by bilateral ECT than in those patients treated by unilateral ECT (14.5 ± 2.5 vs 8.5 ± 1.6) but this was not statistically significant.

**Neurophysin release**

**Basal concentrations and effects of ECT** Figure 4 shows the mean serum neurophysin concentrations before and after the first treatment of the course of ECT in the good outcome group \( (N = 6) \) and the poor outcome group \( (N = 13) \) at two months. The results for total immunoreactive neurophysin (IRN), the vasopressin-associated neurophysin \( (hNpi) \) and the difference (DIFF) between the two (equivalent to the oxytocin-associated neurophysin, \( hNpII \)) are shown separately.

Table IX shows that before ECT serum concentrations of IRN and DIFF were greater in the poor outcome group than in the good outcome group. There was one woman in the poor outcome group in whom DIFF was undetectable before ECT and she was excluded from further calculations involving baseline serum DIFF concentration. There were no statistically significant differences between outcome groups in baseline serum hNpi concentration before ECT. There were no correlations between concentrations of neurophysin before ECT and the severity of depression measured on the HRSD or MADRS.
# TABLE IX

Mean (± SEM) neurophysin concentrations (ng/ml) before ECT by clinical outcome two months after last ECT (with data from Experiment One for comparison)

<table>
<thead>
<tr>
<th>Neurophysin</th>
<th>All patients</th>
<th>Phenothiazine-free patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Poor (n = 13)</td>
<td>Good (n = 6)</td>
</tr>
<tr>
<td>IRN</td>
<td>0.8 ± 0.1(^b)</td>
<td>0.4 ± 0.3</td>
</tr>
<tr>
<td>hNpI</td>
<td>0.2 ± 0.0</td>
<td>0.2 ± 0.1</td>
</tr>
<tr>
<td>DIFF (hNpII)</td>
<td>0.6 ± 0.1(^a, b)</td>
<td>0.2 ± 0.1</td>
</tr>
</tbody>
</table>

**Experiment One**

<table>
<thead>
<tr>
<th></th>
<th>Poor (n = 9)</th>
<th>Good (n = 16)</th>
<th>Poor (n = 6)</th>
<th>Good (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESN(^c)</td>
<td>1.8 ± 0.2(^b)</td>
<td>1.3 ± 0.1</td>
<td>1.7 ± 0.2(^b)</td>
<td>1.2 ± 0.1</td>
</tr>
</tbody>
</table>

\(^a\) n = 12. In one patient, DIFF was undetectable before ECT.

\(^b\) Significantly (p < 0.05) greater than concentration in the good outcome group.

\(^c\) Converted from pmol/l; 1 ng/ml = 80 pmol/l

The normal values (± SEM) of IRN for healthy people of similar average age are 2.4 ± 0.2 ng/ml for women and 1.6 ± 0.2 ng/ml for men.

hNpII constitutes 50% of IRN in men and 15-50% in women depending on phase of the menstrual cycle (Legros, 1975).

The maximum serum concentrations of IRN and DIFF were seen 2.5 min after ECT. Serum concentrations of IRN and DIFF had almost returned to baseline values by 60 min after treatment. There was no clear peak in the release of hNpI but the pattern of release was similar to IRN and DIFF.
Analysis of variance for repeated measures revealed significant effects of time in both conventional and conservative F tests for the release of the neurophysins. In the conservative F test for IRN, $F = 24.1$, d.f. 1, 18, $p < 0.01$; hNPi; $F = 10.0$, d.f. 1, 18, $p < 0.01$ and DIFF, $F = 21.0$, d.f. 1, 18, $p < 0.01$. The conventional F test revealed significant effects of a group-time interaction for IRN and DIFF, but neither of these effects was significant in the conservative F test.

Effects of drug exposure One factor contributing to the baseline differences in serum IRN and DIFF concentration between outcome groups was the different phenothiazine exposure in the two groups. The mean baseline serum IRN and DIFF concentrations were significantly lower in those taking phenothiazines. In the 11 phenothiazine-free patients mean baseline IRN concentration was $0.88 \pm 0.1$ ng/ml, but in the eight patients taking phenothiazines, mean baseline IRN concentration was only $0.41 \pm 0.1$ ng/ml ($p < 0.01$). Mean baseline DIFF concentration was three times greater in phenothiazine-free patients than in those patients taking phenothiazines ($0.63 \pm 0.1$ ng/ml versus $0.22 \pm 0.1$ ng/ml, $p < 0.01$). A greater proportion of the patients in the good outcome group received phenothiazines compared with patients in the poor outcome group (four out of six patients versus four out of 13). Table IX also shows the baseline neurophysin concentrations in those patients who were free of phenothiazine drugs. Although there is a trend for the baseline neurophysin concentrations of IRN and DIFF to be lower in those with a good outcome, there were only two patients in the good outcome group who were free of phenothiazines and it would be incautious to draw any conclusions from such a small sample.
There was no difference in serum neurophysin concentrations between those patients taking and not taking tricyclic antidepressants.

Clinical outcome Table X shows the relationship between percentage peak increases in serum concentrations of the neurophysins after the first ECT and clinical outcome two months after ECT. The release of IRN was more than twice as great in the good outcome group compared to the poor outcome group and this was the result of a much greater release of DIFF in the good outcome group. The relation between neurophysin release against clinical outcome was strongest for the release of DIFF. The release of DIFF after the first ECT in the good outcome group was four times that of those in the poor outcome group two months after the last ECT. Figure 5 shows the relationship between the percentage peak increase in serum DIFF concentration over mean concentration before ECT plotted for individual patients against clinical outcome 7-10 days and two months after the last ECT of a course. There is little overlap between the values of percentage peak increase in serum DIFF concentration in the good and poor outcome groups. If a 500% increase in serum DIFF concentration had been used as a cut-off point to define good and poor outcome groups, then one out of 18 patients would have been misclassified by outcome at two months. In one patient DIFF was undetectable before ECT. The overall predictive accuracy of this classification would have been 89%. 

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TABLE X

Relationships between mean (± SEM) neurophysin release\(^a\) after first ECT and clinical outcome\(^b\) two months after last ECT

<table>
<thead>
<tr>
<th>Neurophysin</th>
<th>Outcome</th>
<th>Good ((N = 6))</th>
<th>Poor ((N = 13))</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRN</td>
<td></td>
<td>590 ± 80(^c)</td>
<td>240 ± 53</td>
</tr>
<tr>
<td>hNpI</td>
<td></td>
<td>236 ± 48</td>
<td>202 ± 39</td>
</tr>
<tr>
<td>DIFF (hNpII)</td>
<td></td>
<td>837 ± 100(^d)</td>
<td>202 ± 51(^e)</td>
</tr>
</tbody>
</table>

\(^a\) Percentage peak increase over mean concentration before ECT

\(^b\) See Methods for categorization of outcome

\(^c\) Significantly \((p < 0.01)\) greater than value in poor outcome group

\(^d\) Significantly \((p < 0.001)\) greater than value in poor outcome group

\(^e\) \(N = 12\); in one patient DIFF was undetectable before ECT

**Clinical improvement** Serum neurophysin concentrations before ECT were not correlated with the extent of improvement on HRSD or MADRS. Table XI shows that the percentage peak increase in serum DIFF concentration correlated significantly both with absolute improvement in the HRSD score \((r = 0.50, p < 0.05)\) and the absolute improvement in the MADRS score \((r = 0.47, p < 0.05)\). There were no significant correlations between the increases in serum concentrations of IRN or hNpI and clinical improvement.
Figure 5. Relationship between percentage peak increase in serum DIFF concentration (hNpII) after first treatment of a course of ECT and clinical outcome 7-10 days and 2 months after the last ECT.
TABLE XI

Correlations (Pearson's method) between neurophysin release\textsuperscript{a} after first ECT and clinical improvement\textsuperscript{b}

<table>
<thead>
<tr>
<th>Neurophysin</th>
<th>HRSD</th>
<th>MADRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRN</td>
<td>0.40</td>
<td>0.12</td>
</tr>
<tr>
<td>hNpI</td>
<td>0.16</td>
<td>0.22</td>
</tr>
<tr>
<td>DIFF (hNpII)</td>
<td>0.50 \textsuperscript{c}</td>
<td>0.47 \textsuperscript{c}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Percentage peak increase above mean baseline

\textsuperscript{b} Change in score on rating scale between day before first ECT and 7-10 days after last ECT

\textsuperscript{c} p < 0.05

Cerebral seizure activity

Reliability of measures The 19 EEG records were read by the main EEG rater and also by three other independent raters who had a special interest in neurology or electrophysiology. The inter-rater agreement between the four raters was estimated by Pearson product moment correlations after normalization by a logarithmic transformation. Table XII shows that there were close correlations among all the raters in all three measures of cerebral seizure activity.
### TABLE XII

Correlations (Pearson's method) between main rater and three other independent raters in measurements of cerebral seizure activity (19 EEG records)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Rater 2</th>
<th>Rater 3</th>
<th>Rater 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral spike wave</td>
<td>0.87</td>
<td>0.96</td>
<td>0.92</td>
</tr>
<tr>
<td>Last spike wave</td>
<td>0.87</td>
<td>0.96</td>
<td>0.96</td>
</tr>
<tr>
<td>Total seizure length</td>
<td>0.95</td>
<td>0.95</td>
<td>0.97</td>
</tr>
</tbody>
</table>

All p values < 0.001

**Effects of ECT**

The mean (+ SEM) length of bilateral spike-wave activity was $49.4 \pm 10.1$ s (range 4-137 s), the mean time to the last spike wave was $60.0 \pm 10.2$ sec (range 4-138), and the mean length of total cerebral seizure activity was $62.4 \pm 10.5$ sec (range 19-150). There were no significant differences in the EEG measures of cerebral seizure activity between unilateral or bilateral electrode placement, nor between the good and poor outcome groups.

**Relation to neurophysin release**

Table XIII shows that there were no significant correlations between the EEG measures of cerebral seizure activity and the release of the neurophysins.
Electrode placement

There was a non-significant trend for unilateral electrode placement to be associated with a greater release of DIFF (hNpII) than in bilateral electrode placement. The mean percentage peak increase in serum DIFF concentration was $81\% \pm 46\%$ in those treated with unilateral electrode placement ($N = 9$) and $52\% \pm 145\%$ in those treated with bilateral electrode placement ($N = 10$). There were no significant differences or trends in the release of hNpI and IRN between those patients treated with unilateral and bilateral electrode placement.

**TABLE XIII**

Correlations (Pearson's method)\(^a\) between neurophysin release\(^b\) and EEG measures of cerebral seizure activity at first ECT ($N = 19$)

<table>
<thead>
<tr>
<th>EEG measure</th>
<th>Neurophysin</th>
<th>Bilateral spike waves</th>
<th>Last spike wave</th>
<th>Total seizure activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRN</td>
<td>0.09</td>
<td>0.10</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>hNpI</td>
<td>-0.14</td>
<td>-0.12</td>
<td>-0.07</td>
<td></td>
</tr>
<tr>
<td>DIFF (hNpII)(^c)</td>
<td>-0.03</td>
<td>-0.01</td>
<td>-0.03</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Correlations were assessed after logarithmic transformation of EEG measures. None was statistically significant.

\(^b\) Percentage peak increase over mean concentration before ECT.

\(^c\) $N = 18$; DIFF was undetectable in one patient before ECT.
Hypotheses

1. The first hypothesis that ECT induces a rapid rise in serum concentrations of vasopressin- (hNpI) and oxytocin-associated neurophysin (hNpII) as measured by the RIA developed by Legros was supported. The timecourse and magnitude of the change in serum neurophysin concentrations was similar to that described in the first experiment.

2. The hypothesis that the percentage peak increase in serum hNpII concentration after the first ECT correlates with the extent of eventual improvement from ECT was supported. The correlation may be sufficiently close to be of clinical utility in the prediction of recovery after ECT.

3. There was no support for the third hypothesis that the increase in serum hNpII concentration after ECT correlates with the duration of spike-wave activity or total cerebral seizure activity measured by simultaneous EEG recording.

Other Findings

hNpI release There was no correlation between the release of hNpI and cerebral seizure activity nor the extent of improvement from depressive illness. In a study of nine depressed patients, Whalley et al. (1937) found no relationship between the release of NSN, the vasopressin-
associated neurophysin as measured in the Robinson RIA, and the extent of improvement measured by change in HRSD score. Since vasopressin-associated neurophysin may be released by anaesthesia and/or surgery (North et al., 1980; Whalley et al., 1987), its release is not specific to the induction of cerebral seizure activity.

**Baseline neurophysin concentrations** An unexpected finding (in these 19 unipolar depressed patients) was that the baseline serum IRN concentration was about half the average value for age- and sex-matched controls. This was an unexpected finding because no similar trend was found in Experiment One and Legros et al. (1983) have reported normal concentrations of hNpII in the CSF of unipolar depressed patients when compared with a control group of neurological patients. One cause for the depression of baseline IRN concentration was the intake of phenothiazine drugs. Chlorpromazine at a daily dose of 100 mg has been shown to inhibit the stimulatory action of ethinyl oestradiol on the release of IRN (Legros et al., 1975). A separate analysis was conducted in those patients who were free of phenothiazine drugs (N = 11) which found a trend for those patients who had a good outcome at two months to have a lower serum concentration of DIFF and IRN before ECT. Most of the sample were women and the stage of the menstrual cycle is a confounding effect on serum hNpII concentrations; serum hNpII concentration is relatively depressed during the follicular phase (Legros, 1975). The numbers are small and no firm conclusions can be drawn. However, a similar, if less marked, trend was also seen in the 18 patients free of phenothiazine drugs in Experiment One. Serum concentrations of IRN and hNpII before ECT were not correlated with the severity of depression, nor were they useful in the prediction of outcome after ECT. The relationship between
the presence of depressive illness and serum concentrations of IRN and DIFF can be studied in a longitudinal study, when serum neurophysin concentrations can be measured during depressed and recovery phases of the illness. There was no significant difference between outcome groups in baseline serum hNpI concentration.

Comparison of results between experiments No study has compared the two neurophysin assays in the same patients. Legros has not provided conversion factors to convert results in his RIA to molar concentrations. Instead, the data from the Robinson assay in Experiment One were converted to ng/ml and were shown in Table IX for comparison. The plasma ESN concentrations in both the poor and good outcome groups in Experiment One were greater than the serum hNpII concentrations in the present experiment. The sample sizes are small and it would be inappropriate to conclude these differences would still be apparent if larger samples were used. The observed differences between the experiments may be the result of factors pertaining to the patients or to the assays. There is little difference between the patients in age, sex, severity of depression and intake of phenothiazine drugs, and it may be that most of the variance is explained by factors pertaining to the assays. This would be established by direct comparison of serum neurophysin concentrations in blood samples drawn from the same patients, but this will not be possible in the present experiments as the reagents for the Robinson assay are no longer available locally.

Although the validity of each neurophysin RIA as a measure of oxytocin release has been established separately, no study has simultaneously compared results from the two neurophysin RIAs with
results from the assay of oxytocin itself. It would be interesting to compare the correlations of the release of the oxytocin-associated neurophysin and oxytocin itself after the first ECT and the extent of improvement from depressive illness. Unfortunately, this will not be possible in the present experiments as there is no assay for oxytocin available locally.

The major importance of the present findings is that the correlation of the release of the oxytocin-associated neurophysin with improvement has been confirmed using an alternative assay for the neurophysins and in an independent laboratory.

Measures of seizure activity

The inter-rater reliability for all the measures of cerebral seizure activity was high, and it was possible to discriminate between generalized and focal spike-wave activity. The validity of using electrodes attached to the scalp to measure seizure activity in the brain has been questioned (Goldensohn, 1979). Spike-wave activity in the brain which does not affect large areas of cortex will fail to be detected in EEG recordings using scalp electrodes. Goldensohn (1979) estimates that 20 to 70% of spike waves which can be detected by electrodes applied directly to the cerebral cortex will not appear on an EEG recording using scalp electrodes. It is clear that the EEG measures of cerebral seizure activity are underestimates.

The practical difficulties in finding areas of the scalp to which EEG electrodes can be attached during ECT limits the areas from which the
EEG recording can be made. The occiput is not available because the patient's head rests on a pillow and the temporal areas of the scalp are not available because these must be free for the placement of the treatment electrodes. This is a more minor influence on validity as Brumbeck & Staton (1982) showed, using extensive EEG electrode placements, including naso-pharyngeal electrodes, that in both unilateral and bilateral ECT, the amount and amplitude of spike-wave activity was greatest over anterior and parasagittal areas of the scalp (the areas used in the present experiment).

On average, the EEG rater estimated total cerebral seizure activity lasted about 2 s longer than any spike-wave activity. This finding merits comment if indeed spike-wave activity is the "signature of a seizure" (Martin, 1985). The cerebral origin of synchronous spike-wave activity has been much debated. Two main hypotheses have been proposed to explain the origin of this cerebral activity, namely the "centrencephalic hypothesis" which postulates a primary sub-cortical, upper brainstem and/or thalamic involvement, and the cortical hypothesis which postulates that the origin and propagation is primarily in the cortex (Gloor, 1968). Recent evidence suggests that generalized cerebral seizure activity involves both cortical neurones and subcortical structures (Gloor & Fariello, 1988). Cortical neurones themselves are probably the origin of the spike waves which leads secondarily to involvement of thalamocortical projections which are involved in the inhibition of spike-wave activity. This proposition is compatible with the observation of slow-wave activity at the end of the cerebral seizure activity. Certainly, the break-up of spike-wave activity leading to slow-wave activity at the end of cerebral seizure activity and before the
phase of post-ictal suppression is a consistent finding in EEG studies of ECT (Weiner, 1982; Brumback & Staton, 1982).

The conclusion that the release of the neurophysins is unrelated to the length of spike-wave activity or total seizure length would not be valid if the underestimation of cerebral seizure activity were consistently related to neurophysin release itself; for example, that the most marked underestimation of cerebral seizure activity consistently occurred in those patients who released the greatest amounts of neurophysin. There is no known reason for the two to be related. It is still possible that the release of the oxytocin-associated neurophysin is partly related to cerebral seizure activity in the mid-brain, and that the intensity of this activity is related to clinical improvement. This hypothesis could be tested using more sophisticated measures which can assess subcortical neuronal activity, for example, single photon emission computed tomography (SPECT, Ryding et al., 1988).

Other potential sources of error

Potential sources of error pertaining to the sample, clinical assessment, measurement of hormone release, classification by outcome and the confounding effects of drugs, sex and plasma oestrogen concentration have already been discussed in Experiment One.

The reliability of the Legros RIA is similar to that of the Robinson assay. Which is a more valid measure of oxytocin release has not been assessed.
The development of the methodology in the present experiment involved the use of a newer depression rating scale designed to be sensitive to clinical change during treatment for depression. Like the HRSD, the MADRS has been shown to be of high inter-rater reliability and to be closely correlated with global measures of illness severity in tests of validity (Montgomery & Asberg, 1979).

Spurious correlations may arise with the Pearson product moment correlation if the variables under assessment do not meet the requirements of the method (see Sources of Error, Experiment One). In the present experiment, the Bartlett-Box F test was used to confirm the homogeneity of variances when significant correlations were found.

Explanation of findings

Present hypotheses The simplest explanation of the association between the release of the oxytocin-associated neurophysin and recovery after ECT was that the release of oxytocin-related neurophysin was a sensitive measure of cerebral seizure activity. Those depressed patients in whom ECT led to the most extensive spike-wave activity would fare best with treatment. This hypothesis was not supported by the present findings. The hypothesis that the release of the oxytocin-associated neurophysin is the result of electrical stimulation of neurophysin-containing neurones has not been tested in the present experiment and remains as a possible explanation of the correlation between the release of the oxytocin-associated neurophysin and clinical outcome. (The argument in support of this hypothesis was given at the end of Chapter 3.) This hypothesis would also explain why the release of the
vasopressin-associated neurophysin is not correlated with clinical outcome. The electro-physiological characteristics of oxytocin- and vasopressin-containing magnocellular neurones are distinct (Poulain & Wakerley, 1982). Whereas the release of oxytocin increases with the increase in firing rate of oxytocin-containing neurones, this is not the case with vasopressin-containing neurones in which the release of vasopressin is associated with phasic bursts of electrical discharge. The hypothesis that oxytocin-associated neurophysin release is a correlate of the strength of electrical stimulation reaching the mid-brain was not supported by the trend for unilateral ECT to release more neurophysin than bilateral ECT. This trend was not statistically significant and may not be replicated in a larger sample of patients. Moreover, studies which have detected a difference between unilateral and bilateral electrode placement in their effects on pituitary hormone release, for example, prolactin, have studied the effects of electrode placement sequentially within the same patients rather than by comparisons between different patients treated either by unilateral or bilateral ECT (see Review of the Literature). It is probable that the design of the present experiment was not sufficiently powerful to detect any real difference between unilateral and bilateral electrode placement because of the large standard deviation around mean neurophysin release and the effect size which, if similar to prolactin, will be small (Cohen, 1977).

Development of hypotheses
A second explanation involves the control of the release of oxytocin and its associated neurophysin. Siever & Davis (1985) hypothesized that depressive illness may be understood as a failure of regulation of neurotransmitter systems (the "dysregulation hypothesis of depressive
illness") rather than simple increases or decreases in their activity. Furthermore, they propose that specific stimuli may probe the regulation of neuroendocrine systems (as in endocrine challenge tests, Stokes & Sikes, 1988), and that effective treatments restore efficient regulation. In a subgroup of depressed patients there is a marked increase in the release of oxytocin-associated neurophysin after ECT and this subgroup of depressed patients is more likely to recover after ECT. In terms of the dysregulation hypothesis, ECT acts as a probe and the increased release of the oxytocin- associated neurophysin after ECT reveals a dysregulation in the neural control of neurophysin release.

The neural control of the release of oxytocin and its associated neurophysin has been investigated mainly in rats and other animals, and how much of this data can be extrapolated to human beings must be open to question (see Lincoln & Paisley, 1932; Poulain & Wakerley, 1982, for reviews). The release of oxytocin is associated with an increased firing rate in oxytocin-containing neurones of the hypothalamus. The release of oxytocin may be modified by the activity of a variety of neurotransmitters and peptides. Oxytocin release may be tonically inhibited by endogenous opioid peptides and the stimulation of beta-adrenoceptors can also inhibit oxytocin release. Conversely, stimulation of alpha-adrenoceptors may lead to oxytocin release and pharmacological studies have suggested that acetylcholine, dopamine and oxytocin itself may increase release. A dysregulation which involves one or more of these neurotransmitters may well be relevant to the pathology of depressive illness (see Meltzer, 1987, for review).
An important implication of the dysregulation model of neurophysin release can be assessed in depressed patients. The dysregulation model implies that the release of the oxytocin-associated neurophysin will be rectified in the subgroup of patients who respond to ECT. Such a hypothesis can be tested in a longitudinal study of depressed patients treated by ECT in which the release of the oxytocin-associated neurophysin is measured at the first ECT and at the end of a course of ECT. Any change in neurophysin release can be compared with the extent of improvement in symptoms of depressive illness.

A third explanation is that oxytocin, its associated neurophysin, or a peptide which co-exists with oxytocin in oxytocin-containing neurones (Everitt & Hokfelt, 1986) may have direct antidepressant effects on depressed patients. In other words, those depressed patients in whom ECT led to the greatest release of this peptide with antidepressant properties experienced the greatest benefits from a course of ECT. Many peptide hormones have behavioural effects in addition to their endocrine effects and the "neuroendocrine hypothesis" of the mode of action of ECT assumes that ECT enhances the production and release of a hypothalamic peptide with antidepressant properties (Fink & Nemeroff, 1989), but this third explanation is the most speculative because there are no data on the behavioural effects of oxytocin in depressed patients. (This topic will be developed in the next chapter.)
Three hypotheses have been developed to explain the correlation between the extent of the release of the oxytocin-associated neurophysin after the first ECT and the extent of improvement in depressive illness after a course of treatment. One hypothesis, that oxytocin or a related peptide has direct antidepressant effects, is the most speculative. The other two are that the release of the oxytocin-associated neurophysin is a correlate of the intensity of electrical stimulation reaching the midbrain, and that the release of the oxytocin-associated neurophysin reveals a neural dysregulation in depressed patients who are likely to recover with ECT. If the release of the oxytocin-associated neurophysin were shown to be a correlate of electrical stimulation, this is unlikely to lead to new insights into the mode of action of ECT. However, if the release of the oxytocin-associated neurophysin reveals a biological abnormality, and this biological abnormality is rectified by a course of ECT, then this is more likely to be informative about the mode of action of ECT. This is the hypothesis that will be tested in the next experiment. Moreover, a longitudinal study which measures the release of the oxytocin-associated neurophysin in the same patients at the outset and the end of a course of ECT allows other hypotheses to be tested. First, this is a more powerful design to investigate the relationship between the release of the neurophysins and cerebral seizure activity, as seizure activity is likely to decline towards the end of a course of ECT (Sackeim et al., 1987b). Secondly, a longitudinal study is appropriate to test the hypothesis that depressive illness is associated with a reduction in the serum hNpII concentration.
Aims

The aims of the experiment were:

1. The measurement of the increase in serum hNpII concentration after the first and last treatments in a course of ECT to establish whether the ECT-induced release of hNpII is modified by a course of ECT.

2. The investigation of the relationship between any modification in ECT-induced release of hNpII and (a) the extent of improvement in symptoms of depressive illness, and (b) the expected reduction in cerebral seizure activity that will occur over a course of ECT.

3. The measurement of serum IRN and hNpII concentration before the first and last treatments in a course of ECT to establish whether the basal release of neurophysins is altered between the depressed and recovered phases of depressive illness.
Hypotheses

The following hypotheses were tested:

1. The percentage peak increase in serum hNpII concentration after the last ECT in a course of treatment is less than after the first ECT.

2. The change in the ECT-induced release of hNpII between the first and last treatments is correlated with the extent of improvement in symptoms of unipolar depressive illness measured by change in HRSD and MADRS scores.

3. The change in the ECT-induced release of hNpII between the first and last treatments is correlated with the changes in spike-wave and total cerebral seizure activity measured by simultaneous EEG recording.

4. The serum concentrations of IRN and hNpII are greater before the last ECT than before the first ECT.

Methods

Ethics

The study protocol was approved in advance by the Psychiatry and Clinical Psychology Ethics of Research Sub-Committee of the Lothian Health Board.
Depressed patients

The sample consisted of 17 patients admitted to the Royal Edinburgh Hospital for inpatient treatment of unipolar depressive illness and referred routinely for ECT. The present experiment was planned before Experiment Two was completed. The last seven patients to take part in Experiment Two agreed to allow blood sampling and EEG recording at their last ECT and are included in the present sample. The patients had not received ECT within six months, had no physical illness or symptoms suggestive of organic cerebral disease, and were able to give informed consent and comply with study procedures. None of the patients was hypertensive or obese. There were 12 women (mean age 51.5 ± 4.3, range 28-73 years) and five men (mean age 58.0 ± 3.8, range 44-70 years), and all met RDC for Probable (N = 1) or Definite (N = 16) Major Depressive Disorder. Before the first ECT, only three subjects were drug-free. None of the women was taking an oral contraceptive pill. By agreement with the referring psychiatrist, no changes in drug therapy were made between the first and last treatments.

Clinical assessment

See Experiment Two
The ECT procedures were identical to those in Experiment Two. A course of ECT consisted of an average of 7.4 treatments (range 5-11). Electrical stimulus at the first and last treatments was standard. An Ectron CCX Series 3 ECT machine delivered 850 mA over 5 s in 1.5 ms pulses at a frequency of 45 Hz.

Measures of cerebral seizure activity

See Experiment Two

Blood sampling

The patients in the present experiment were asked to consent to intravenous cannulation on two occasions during the course of ECT. For this reason it was felt appropriate to reduce the length of cannulation to only 30 min after treatment. Patients were not allowed to smoke between cannulation and the time of the last blood sample. An indwelling intravenous catheter was inserted at least 45 min before ECT. Blood samples (5 ml) were taken at 30, 15 and 1 min before treatment and after electrical stimulation at 2.5, 5, 7.5, 10, 12.5, 15 and 30 min. Blood samples were placed immediately in plain tubes and stored at 4°C. Serum was separated by centrifugation and samples stored at -20°C.
Hormone assays

See Experiment Two

Statistics

See Experiment One

Results

Clinical details

Assessment of immediate outcome showed that seven patients had a good outcome and 10 patients had a poor outcome 7-10 days after the last ECT. Two of the patients who had a good outcome 7-10 days after ECT relapsed within two months after the last ECT and were still inpatients. Table XIV shows the clinical details of the patients by outcome group at two months after ECT. There were no significant differences between the two groups before ECT in age, sex, RDC category, or initial HRSD score. The severity of depression before ECT as measured by MADRS score was about eight points higher in the poor outcome group than in the good outcome group. The difference in initial depression rating scores does not explain the difference in final outcome scores as the absolute improvement in HRSD score was significantly greater in the good outcome group \( (19.2 \pm 1.7 \text{ vs } 12.9 \pm 1.9, \ p < 0.05) \) and there was a similar trend in the improvement in MADRS score \( (24.4 \pm 3.1 \text{ vs } 21.6 \pm 2.9, \ NS) \). A greater proportion of the poor outcome group was free of
## TABLE XIV
Clinical details by outcome two months after last ECT

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Good (n = 5)</th>
<th>Poor (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>3M, 2F</td>
<td>2M, 10F</td>
</tr>
<tr>
<td>Age ± SEM</td>
<td>59.8 ± 3.4</td>
<td>50.8 ± 4.7</td>
</tr>
<tr>
<td>RDC category a:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMDD-P</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>DMDD</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>DMDD-P</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Initial HRSD ± SEM</td>
<td>22.2 ± 1.7</td>
<td>24.8 ± 1.5</td>
</tr>
<tr>
<td>Initial MADRS ± SEM</td>
<td>28.8 ± 1.9</td>
<td>37.2 ± 2.1 b</td>
</tr>
<tr>
<td>Antidepressant (AD) failure c</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Drug therapy at 1st ECT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Phenothiazine (PZ)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>AD</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>AD + PZ</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Lithium carbonate</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>ECT: unilateral/bilateral</td>
<td>1/4</td>
<td>7/5</td>
</tr>
<tr>
<td>Number of ECT ± SEM</td>
<td>6.6 ± 0.6</td>
<td>7.8 ± 9.6</td>
</tr>
<tr>
<td>Final HRSD ± SEM</td>
<td>3.0 ± 1.0</td>
<td>11.9 ± 1.7 d</td>
</tr>
<tr>
<td>Final MADRS ± SEM</td>
<td>4.4 ± 1.4</td>
<td>15.7 ± 2.7 e</td>
</tr>
</tbody>
</table>

---

a See Table VIII for meaning of abbreviations
b Significantly (p < 0.05) greater than score in good outcome group
c See Table VIII for definition
d Significantly (p < 0.001) greater than score in good outcome group
e Significantly (p < 0.01) greater than score in good outcome group
psychotropic drugs at the outset of ECT (three of 12 patients versus none of five patients), but the mean improvement in these three patients (HRSD, 17.0; MADRS, 22.7) was at least as good as the improvement in patients who received psychotropic drugs (HRSD, 14.3 ± 1.7; MADRS, 22.4 ± 2.4). A greater proportion of the good outcome group received bilateral ECT (four of five patients versus five of 12 patients), but the mean improvement in those patients who received bilateral ECT (HRSD, 15.7 ± 2.4; MADRS, 23.1 ± 3.5) was not statistically different from those patients who received unilateral treatment (HRSD, 13.8 ± 2.1; MADRS, 21.6 ± 2.9).

Neurophysin release

Basal concentrations and effects of ECT Figure 6 shows the mean serum neurophysin concentrations before and after the first and last treatments of a course of ECT given to 17 unipolar depressed patients. Analysis of variance for repeated measures revealed highly significant effects (p < 0.001) of time for all three measures of neurophysin release at both the first and last treatments in the conventional F tests which were also significant (p < 0.01) in conservative F tests.

There were no significant changes in basal serum neurophysin concentrations before ECT between the first and last treatments.
Figure 6. Serum neurophysin concentrations (mean ± SEM) before and after the first and last treatments in a course of ECT given to 17 unipolar depressed patients.
When serum concentrations of IRN and DIFF (hNpII) were compared between the first and last treatments, there was a trend for serum neurophysin concentrations in the 15 min after ECT to be less at the last ECT than at the first. These were not consistent differences and were only observed in 10 of the 17 patients. Analysis of variance for repeated measures revealed no significant effects of treatment occasion in the conventional F tests, nor were there significant effects for time-occasion interactions for any of the neurophysins. There were no significant differences in percentage peak increase in serum neurophysin concentrations between the first and last treatments.

Basal concentrations and clinical outcome Table XV shows that there were no statistically significant differences between the outcome groups in serum neurophysin concentrations before the first ECT. When the data from the present experiment were pooled with the data from Experiment Two, there were non-significant trends for the basal neurophysin concentrations to be greater in the good outcome group than in the poor outcome group. The sample sizes are small and must be interpreted with caution, but these trends are in the opposite direction to that predicted from the results of Experiments One and Two. There were no significant correlations between basal neurophysin concentrations and illness severity measured by HRSD and MADRS.
TABLE XV

Mean (± SEM) serum neurophysin concentrations (ng/ml) before first ECT by clinical outcome two months after last ECT (with data from Experiment Two)

<table>
<thead>
<tr>
<th>Neurophysin</th>
<th>All patients</th>
<th>Phenothiazine-free patients</th>
<th>Outcome</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Poor</td>
<td>Good</td>
<td>Poor</td>
<td>Good</td>
</tr>
<tr>
<td>IRN</td>
<td>1.4 ± 0.4</td>
<td>1.5 ± 0.6</td>
<td>1.8 ± 0.6</td>
<td>2.1</td>
</tr>
<tr>
<td>hNpI</td>
<td>0.5 ± 0.1</td>
<td>0.6 ± 0.2</td>
<td>0.6 ± 0.1</td>
<td>0.8</td>
</tr>
<tr>
<td>DIFF (hNpII)</td>
<td>1.0 ± 0.4</td>
<td>1.0 ± 0.6</td>
<td>1.3 ± 0.5</td>
<td>1.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neurophysin</th>
<th>Experiments Two and Three</th>
<th>Outcome</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 16</td>
<td>n = 13</td>
<td>n = 10</td>
</tr>
<tr>
<td>IRN</td>
<td>0.8 ± 0.1</td>
<td>1.6 ± 0.4</td>
<td>0.8 ± 0.1</td>
</tr>
<tr>
<td>hNpI</td>
<td>0.3 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.3 ± 0.1</td>
</tr>
<tr>
<td>DIFF (hNpII)</td>
<td>0.5 ± 0.1₁</td>
<td>1.1 ± 0.4</td>
<td>0.6 ± 0.1</td>
</tr>
</tbody>
</table>

The normal values (± SEM) of IRN for healthy people of similar average age are 1.7 ± 0.2 ng/ml in women and 1.6 ± 0.2 ng/ml in men. hNpII constitutes 50% of IRN in men and 15-50% in women depending on phase of the menstrual cycle (Legros, 1975). There were no significant differences between outcome groups.₁ N = 15, in one patient DIFF was undetectable before ECT.
Effects of first ECT and clinical outcome Table XVI shows that there were no significant differences between the outcome groups in the percentage peak increase in serum neurophysin concentrations after the first ECT, nor were there any significant differences when the data from the present experiment were pooled with the data from Experiment Two.

TABLE XVI

Relationship between percentage peak increase in serum neurophysin concentrations (mean ± SEM) after first ECT and clinical outcome two months after last ECT

<table>
<thead>
<tr>
<th>Neurophysin</th>
<th>Experiment Three</th>
<th>Experiments Two and Three</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Outcome</td>
<td>Outcome</td>
</tr>
<tr>
<td>Poor</td>
<td>Good</td>
<td>Poor</td>
</tr>
<tr>
<td>n = 12</td>
<td>n = 5</td>
<td>n = 16</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Experiment Three</th>
<th>Experiments Two and Three</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRN</td>
<td>362 ± 131</td>
<td>280 ± 112</td>
</tr>
<tr>
<td>hNpI</td>
<td>149 ± 33</td>
<td>137 ± 40</td>
</tr>
<tr>
<td>DIFF (hNpII)</td>
<td>705 ± 362</td>
<td>622 ± 205</td>
</tr>
<tr>
<td></td>
<td>344 ± 106</td>
<td>334 ± 70</td>
</tr>
<tr>
<td></td>
<td>178 ± 30</td>
<td>156 ± 26</td>
</tr>
<tr>
<td></td>
<td>607 ± 292</td>
<td>570 ± 135</td>
</tr>
</tbody>
</table>

There were no significant differences between outcome groups.

aN = 15, in one patient DIFF was undetectable before ECT.
When individual values of percentage peak increase in serum hNpII concentration were plotted by outcome group for the data in the present experiment and for the pooled data, there were considerable overlaps between the outcome groups. (This was also the case when patients were classified by outcome 7-10 days after the last ECT; these data are not shown.) If a 500% rise in serum hNpII concentration was used to classify all patients by outcome 7-10 days after the last ECT, then six patients were misclassified and in one patient the percentage peak increase could not be calculated. This gives a predictive accuracy of 76% for immediate outcome. If a 500% increase in serum hNpII concentration was used to classify all patients by outcome two months after the last ECT, then eight patients were misclassified and in one patient the percentage increase could not be calculated. This gives a predictive accuracy of 69% for outcome two months after the last ECT. The estimate of predictive accuracy was no greater when patients who took phenothiazine drugs were excluded.

hNpII release after a course of ECT and clinical outcome Figure 7 shows mean serum hNpII concentrations before and after the first and last treatments in a course of ECT in the good (n = 5) and poor (n = 12) outcome groups at two months. When the percentage peak increases in serum hNpII concentration at the first and last treatments were compared separately for the good and poor outcome groups, there were no significant differences between the treatments in either outcome group. Nor were there any significant differences in the release of IRN or hNpl between the first and last treatments when these comparisons were made separately for the two outcome groups.
Figure 7. Mean serum hNpII concentrations (mean + SEM) before and after the first and last treatments in a course of ECT in the good (n = 5) and poor (n = 12) outcome groups at two months.
Basal concentrations and clinical improvement There were no significant correlations between serum neurophysin concentrations before the first ECT and the extent of clinical improvement over a course of ECT.

Effects of first ECT and clinical improvement Table XVII shows that there were significant correlations between the percentage peak increase in serum IRN concentration after the first ECT and clinical improvement as measured by change in HRSD and MADRS scores. These correlations were the result of significant correlations between the release of hNpII after the first ECT and clinical improvement.

Table XVII also shows the pooled data for Experiments Two and Three and the closeness of the correlations are similar. The correlations for the pooled data were also examined in those patients free of phenothiazine drugs (n = 16). The correlations between the percentage peak increase in serum IRN concentration and improvement were $r = 0.63$ ($p < 0.01$) for HRSD score and $r = 0.66$ ($p < 0.01$) for MADRS score. These correlations were the result of close correlations between the percentage peak increase in serum hNpII concentration and clinical improvement ($r = 0.62, p < 0.01; r = 0.63, p < 0.01$).

The correlations for the pooled data were also assessed separately in men (n = 8) and women (n = 21). It was not appropriate to use Pearson's method in the men because of the small sample size; the correlations (Spearman's method) between percentage peak increase in serum hNpII concentration and improvement were $\rho = 0.44$ (NS) for HRSD score and $\rho = 0.52$ (NS) for MADRS score. In women, the correlations...
(Pearson's method) were \( r = 0.60 \) (\( p < 0.01 \)) for HRSD score and \( r = 0.47 \) (\( p < 0.05 \)) for MADRS score.

There were no significant correlations between the percentage peak increase in hNpI concentration and clinical improvement.

**TABLE XVII**

Correlations (Pearson's method) between percentage peak increase in serum neurophysin concentrations after first ECT and clinical improvement

<table>
<thead>
<tr>
<th>Neurophysin</th>
<th>Experiment Three ((n = 17))</th>
<th>Experiment Two and Three ((n = 29))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rating scale</td>
<td>Rating scale</td>
</tr>
<tr>
<td>IRN</td>
<td>HRSD 0.55(^b) MADRS 0.47(^b)</td>
<td>HRSD 0.52(^c) MADRS 0.42(^b)</td>
</tr>
<tr>
<td>hNpI</td>
<td>-0.19</td>
<td>-0.06</td>
</tr>
<tr>
<td>DIFF (hNpII)</td>
<td>0.52(^b) HRSD 0.44(^b)</td>
<td>0.53(^c) MADRS 0.44(^b)</td>
</tr>
</tbody>
</table>

\(^a\) Change in score on rating scale between day before first ECT and 7-10 days after last ECT

\(^b\) \( p < 0.05 \)

\(^c\) \( p < 0.01 \)
hNpII release after a course of ECT and clinical improvement Between the first and last treatments, the percentage peak increase in serum hNpII concentration fell in 10 patients, rose in five patients and was unchanged (the difference was less than 10%) in two patients. There were no significant differences in improvement in HRSD or MADRS score between the patients in whom the increase in serum hNpII concentration fell and the patients in whom the increase in serum hNpII concentration rose. The mean reduction in HRSD score was 15.5 ± 2.2 in patients in whom the increase in serum hNpII concentration fell and 13.8 ± 3.1 in patients in whom the increased serum hNpII concentration rose. The mean reduction in HRSD score was 13.5 in the two patients in whom the increase in serum hNpII concentration was unchanged.

There were no significant correlations between alterations in percentage peak increases in serum neurophysin concentrations between the first and last treatments and clinical improvement.

Cerebral seizure activity

Between the first and last treatments, there were no significant changes in any of the measures of cerebral seizure activity, although there was a non-significant trend for cerebral seizure activity to fall. At the first ECT, the mean lengths of cerebral seizure activity were 29.8 ± 3.1 s (bilateral spike waves), 33.4 ± 4.2 (last spike wave), and 41.3 ± 6.5 s (total seizure length). At the last ECT, the mean lengths of cerebral seizure activity were 28.7 ± 8.1 s, 30.7 ± 8.3, and 38.2 ± 8.7 s. Between the first and last treatments, total cerebral seizure activity fell in nine patients, rose in three patients and was unchanged.
in five patients (change less than 1 s).

**Clinical outcome** There were no significant differences in any of the measures of cerebral seizure activity between the good and poor outcome groups at the first ECT, the last ECT nor in changes between the first and last treatments.

**Relationship to neurophysin release** There were no significant correlations between any of the EEG measures of cerebral seizure activity and the percentage peak increases in serum concentrations of the neurophysins after the first or last ECT. Table XVIII shows that there were no significant correlations between changes in the release of the neurophysins and changes in cerebral seizure activity between the first and last treatments.

**Electrode placement and neurophysin release**

There were no significant differences in the mean percentage peak increases in serum neurophysin concentrations between those patients treated by unilateral ECT and those patients treated by bilateral ECT at either the first or last treatments. The mean percentage peak increase in serum hNP II after the first ECT was 660 ± 522% in those patients treated with unilateral electrode placement (n = 8) and 699 ± 201% in those patients treated with bilateral electrode placement (n = 9). A similar non-significant trend was present in the pooled data. The mean percentage peak increase in serum hNP II was 531 ± 320% in those patients treated by unilateral ECT (n = 13) and 620 ± 143% in patients treated by bilateral ECT (n = 16).
TABLE XVIII

Correlation (Pearson's method) between altered neurophysin release and cerebral seizure activity between first and last treatments in a course of ECT (n = 17)

<table>
<thead>
<tr>
<th>Neurophysin</th>
<th>Bilateral spike waves</th>
<th>Last spike wave</th>
<th>Total seizure length</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRN</td>
<td>0.23</td>
<td>0.26</td>
<td>0.21</td>
</tr>
<tr>
<td>hNpI</td>
<td>-0.14</td>
<td>-0.12</td>
<td>-0.12</td>
</tr>
<tr>
<td>DIFF (hNpII)</td>
<td>0.25</td>
<td>0.20</td>
<td>0.18</td>
</tr>
</tbody>
</table>

None of the correlations was statistically significant.

Comment

Hypotheses

1. There was no support for the hypothesis that the peak percentage increase in serum hNpII concentration after ECT falls between the first and last treatments in a course of ECT. Nor was there any support for the hypothesis when it was tested in the good and poor outcome groups separately. Thus, there was no support for the hypothesis that the ECT-induced release of hNpII is modified by a course of ECT.
2. There was no support for the hypothesis that any difference in the ECT-induced release of hNpII between the first and last treatments of a course of ECT correlates with the extent of improvement in symptoms of depressive illness. This was not simply a failure to detect a correlation because of an inadequate sample size; there was no difference in clinical improvement between those patients in whom the ECT-induced release of hNpII rose over a course of treatment and those patients in whom the release of hNpII fell.

3. There was no support for the hypothesis that any change in the ECT-induced release of neurophysins between the first and last treatments correlates with changes in EEG measures of cerebral seizure activity. This is further confirmation that there is no association between neurophysin release and cerebral seizure activity measured by EEG recording using scalp electrodes.

4. There was no support for the hypothesis that the basal serum concentrations of IRN or hNpII rise between the first and last treatments of a course of ECT. Nor was there any support for this hypothesis when it was tested in the good and poor outcome groups separately. Thus, there was no support for the hypothesis that recovery from depressive illness is associated with an increase in serum concentrations of IRN or hNpII.
Other findings

**hNpII release after first ECT and clinical improvement** The findings from the pooled data showed that the correlation between hNpII release after the first ECT and clinical improvement exists in men and women separately, and in patients free of phenothiazine drugs. There was, however, a considerable overlap in the release of hNpII at the first ECT between patients who recovered after ECT and those who did not. The predictive accuracy of hNpII release as a predictor of recovery after ECT would have been no better than prediction based on the presence of the typical features of depressive illness (Katona & Aldridge, 1984; Andrade et al., 1988).

**Basal serum neurophysin concentrations and clinical outcome** An unexpected finding in the previous experiments was that those patients who had a good outcome after ECT tended to have a lower basal serum oxytocin-associated neurophysin concentration than those patients with a poor outcome. This trend was more marked when outcome was assessed two months after the last ECT. This unexpected finding was treated with caution because of the small number of patients free of the confounding effect of the intake of phenothiazine drugs. In the pooled data from Experiments Two and Three, no such trend was seen. In addition, the mean basal serum IRN concentration before the first ECT (1.2 ng/ml) in those depressed patients free of phenothiazine drugs (N = 16) was closer to the normal values reported by Legros (1975).
Potential sources of error

Potential sources of error in sampling, clinical assessment, measurement of hormone release and the EEG measures of cerebral seizure activity have already been discussed in previous experiments. The misclassification of patients by recovery, because patients with a poor outcome had had insufficient treatment (see Experiment One), may lead to an underestimation of the predictive accuracy of hNpII release in the prediction of recovery. There were two patients in the poor outcome group at 7-10 days after the last ECT in whom there were substantial rises in serum hNpII concentrations. It is possible they would have recovered fully had they had further ECT, but as they had already had more than the average number of ECT, this is less likely. One way to minimize this source of error is to insist that patients who have made little improvement during a course of ECT receive an adequate minimum number of treatments. What constitutes an adequate course of ECT cannot be specified in advance for any one patient. It has been recommended that up to 12 treatments be administered before it is decided to terminate the course of ECT because of lack of efficacy (ECT Sub-Committee of the Royal College of Psychiatrists, 1989). The inclusion of such a requirement in the protocol of an ECT study is unlikely to be acceptable to a substantial proportion of patients and their psychiatrists.

Potential sources of error because of the intake of psychotropic drugs have also been discussed in the previous experiments. No changes in the intake of psychotropic drugs occurred during any of the courses of
ECT (see Methods) and the lack of support for the hypothesis that the release of hNpII would be modified by a course of ECT is not the result of alterations in the intake of psychotropic drugs.

Explanation of findings

Three explanations were suggested after Experiment Two for the correlation between the release of oxytocin-associated neurophysin after the first ECT and the extent of eventual improvement in symptoms of depressive illness after a course of ECT. The hypothesis that the ECT-induced release of hNpII revealed a neural dysregulation in the control of the release of oxytocin and its associated neurophysin and that this dysregulation would be rectified by a course of ECT was not supported. The release of hNpII did not change between the first and last treatments in a course of ECT and this finding applied both to patients who recovered and those who did not after a course of treatment.

The likeliest explanation for the correlation between hNpII release and clinical improvement is that the release of hNpII is a sensitive measure of the intensity of electrical stimulation reaching the midbrain and the amount by which the intensity of stimulation exceeds seizure threshold is an important influence in the antidepressant efficacy of the induced seizure. The electrical stimulus at the first and last treatments was standard in the present experiment and thus the finding that the release of hNpII did not change between the first and last treatments is further support for this explanation. Computer simulation of the current density in unilateral and bilateral ECT suggests that the current density in the midbrain during unilateral ECT is only about two-
thirds of the current density during bilateral ECT (Weaver et al., 1976). In the present experiment, only a slight and non-significant trend was found for bilateral ECT to be associated with a greater release of hNpII than unilateral ECT. However, in view of the many influences on the release of pituitary hormones and the great variability in hormone release among depressed patients, the design of the present experiment was insufficiently powerful to detect any difference between unilateral and bilateral ECT in their effects on hNpII release (see Experiment Two).

A third, and the most speculative, explanation concerned the "neuroendocrine hypothesis" of ECT (Fink & Nemeroff, 1989). The hypothesis is based on the diabetes-insulin model and suggests that hypothalamic dysfunction with an insufficiency of a mood-maintaining peptide is the basis of depressive illness. Repeated seizures enhance the production and release of a hypothalamic peptide ("antidepressin") which relieves both neuroendocrine and behavioural abnormalities. The identity of any such hypothalamic peptide with antidepressant properties has not been established. Speculation based on the present findings is that the oxytocin-associated neurophysin, oxytocin itself, or a peptide released at the same time has antidepressant properties.

Oxytocin and the neuroendocrine hypothesis of ECT Oxytocin-containing neurones are widely distributed in the CNS of animals and man (Buijs, et al., 1985; Robinson, 1986). Most oxytocin-containing neuronal projections from magnocellular neurones in the paraventricular and supraoptic nuclei of the hypothalamus project to the posterior pituitary. However, oxytocin-containing projections from parvocellular neurones in the paraventricular nucleus project to many areas of the
brain, including the limbic system, brainstem and spinal cord. It is presumed that oxytocin can be released and act as a neurotransmitter in the CNS, but the physiological role of these oxytocin-containing neuronal projections has not been established. Release of oxytocin from the posterior pituitary can occur independently of release from the CNS into the CSF (Robinson, 1986), thus changes in serum oxytocin concentration need not reflect changes of oxytocin release in the CNS. Electrical stimulation of the hypothalamus has been shown to increase CSF oxytocin concentration (Robinson, 1986), and it is likely that ECT leads to an enhanced release of oxytocin from both the posterior pituitary and within the CNS.

The oxytocin-associated neurophysin has no established physiological role (Robinson, 1978). The established physiological roles for oxytocin include milk ejection (Lincoln & Paisley, 1982) and partuition (Fuchs et al., 1983). Human sexual activity increases the release of oxytocin but the functional significance is unknown (Carmichael et al., 1987). Several other functions have been proposed for oxytocin, including the regulation of sodium balance and the control of the release of peptides from the hypothalamus and pituitary (Chard, 1985). Robinson (1986) noted that the physiological significance of these proposed functions for oxytocin was unclear and concluded that oxytocin had no established hormonal function in men.

Oxytocin may have direct effects on depressive symptoms by its effects either on learning or memory. In animals, oxytocin facilitates the extinction of conditioned behaviours (Kovacs & Telegedy, 1982) and, in humans, impairs learning in healthy volunteers (Fehm-Wolfsdorf et
Al. (1984). Amnseau et al. (1987) have argued that oxytocin has amnesic properties which may facilitate the extinction of maladapted behaviour. They reported the effects of intranasal oxytocin in a patient suffering from obsessive-compulsive disorder; initially, there was a reduction in anxiety and compulsive thoughts, but later, the patient complained of marked memory disturbance and developed delusions of persecution.

Increased activity of the HPA during depressive illness has received considerable attention for over 20 years (see Review of the Literature). Gold et al. (1984) have suggested that depressive illness may be associated with hypersecretion of corticotrophin-releasing factor (CRF); CRF may stimulate not only the pituitary adrenal axis, but may also influence several aspects of brain function to produce depressive symptoms. In animals, oxytocin enhances ACTH release to certain stressful stimuli, but in humans, it inhibits ACTH release (Gibbs, 1986). This is one example of how oxytocin may modify the action of CRF. Oxytocin may modify other biological effects of CRF to reduce the symptoms of depressive illness. Oxytocin co-exists with some CRF-containing neurones in the posterior pituitary (Everitt & Hokfelt, 1986).

Co-existence of neurotransmitters Several neurotransmitters may co-exist within the same neurone. There is still some uncertainty about which neurotransmitters co-exist with oxytocin in the hypothalamus and posterior pituitary (Lightman, 1988). The most consistent report is that of the co-existence of met-enkephalin in the posterior pituitary, but there have also been reports concerning dynorphin, cholecystokinin and
There are no data to suggest that any of these peptides has antidepressant properties (Post et al., 1988).

The hypothalamic peptide whose putative antidepressant properties have been most extensively investigated is TRH (Widerlov, 1988). This interest was the result of the abnormalities found in the TRH stimulation test in a proportion of depressed patients (see Review of the Literature). Oxytocin and TRH are not known to co-exist, but TRH, like oxytocin, is found in neurones outside the hypothalamus (Everitt & Hokfelt, 1986). That electrical stimulation of the mid-brain leads directly to oxytocin release is only a hypothesis, but it has been shown in the rat that electrical stimulation of the paraventricular area increases the release of TRH in the hypothalamus (Rondeel et al., 1989). Moreover, ECS increases the content of TRH in hippocampus, pyriform cortex and amygdala in rats (Kubek et al., 1985) and these changes persist for six to 12 days after three ECS (Sattin et al., 1987). No effect of ECT on plasma TRH concentration was detected in the six minutes after ECT by Whalley et al. (1982), but the length of blood sampling may have been insufficient to detect any change in plasma TRH concentration. The antidepressant properties of both orally and intravenously administered TRH have been studied in several investigations (Widerlov, 1988) and most studies have found no consistent antidepressant effect. The access of peptide hormones to the CNS is limited by the capillary endothelial type junctions and associated capillary peptidase activity that characterizes cerebral vessels (Lightman & Everitt, 1986) and it may be that only a tiny proportion of administered TRH reached CNS. A recent report (Banki et al., 1988) that the CSF concentration of TRH is greater in depressed patients than
in a comparison group of patients suffering a variety of peripheral neurological diseases would not support the hypothesis that depressive illness is associated with a deficiency of TRH in the CNS.

In conclusion, if "antidepressin" exists, its identity is unknown.
CHAPTER SIX

CONCLUSIONS

Methodological considerations

Human studies

The major advantage of the present design is that hypotheses can be tested in depressed human beings, not just in laboratory animals. The major finding depended on the ability to measure the degree of improvement in symptoms of depressive illness and it is hard to imagine that this finding could be replicated in any available animal model of depression. The major disadvantages of studies in human beings are the presence of more confounding effects and less direct methods of measurement than in animal studies. Most depressed patients have taken psychotropic drugs and it is not practical to have direct access to the CNS in human beings in ECT research. If the main aim of an experiment is explanatory, then the experiment should be designed in such a way as to minimize the number of confounding effects. An important aim of the present experiments was to assess the predictive accuracy of a biological measure in the prediction of ECT outcome in the everyday practice of ECT. If the present experiments had been designed, for example, to remove the confounding effects of the intake of psychotropic drugs, then it may not have been possible to generalize the findings to clinical practice.
Measurement of hormone release

There is still no general agreement about how best to measure hormone release after ECT. Once the pattern of hormone release had been described reliably by frequent blood sampling, it was possible to quantify hormone release by the percentage peak increase above mean baseline and obtain reproducible results. The results were consistent with those results when hormone release was measured by absolute increase and increase in area under the time/concentration curve. The method ignores the rate of elimination of hormone from plasma, and will be an underestimate of total hormone release. In a parallel study, a kinetic model which takes into account the elimination of hormone was assessed, but its reliability was poor.

Alterations in plasma hormone concentrations cannot be assumed to measure hormone release beyond the blood-brain barrier in the CNS. Confirmation that oxytocin and its associated neurophysin are released in the CNS after induced seizures will depend on studies of ECS.

Cerebral seizure activity

It is practicable to measure reliably unilateral and bilateral spike-wave activity as well as total cerebral seizure activity by EEG recording with scalp electrodes. Some methods to measure cerebral seizure activity are unreliable and cannot estimate seizure generalization which may be an important influence on hormone release and the antidepressant efficacy of ECT. Although an improvement, EEG recording with scalp
electrodes underestimates cerebral seizure activity and cannot measure specifically seizure activity in subcortical brain structures.

Clinical assessment

The method of clinical assessment distinguished improvement in symptoms of depressive illness during a course of ECT from the absence of residual symptoms after the course of ECT. Improvement, but not recovery, was consistently correlated with oxytocin-associated neurophysin release after the first ECT. Improvement during a course of ECT may be more closely correlated with the biological changes that occur during treatment than outcome in the weeks after treatment when personality and environmental factors are important influences. Important biological differences may exist between those patients who recover after ECT and those who do not. Future studies should assess both clinical improvement and classify patients by final outcome. The present design used a stringent definition of recovery similar to that developed by the NIMH. The recovery rate (29 out of 54 patients, 54%) was not nearly as encouraging as many reports in the ECT literature. The lack of agreement about the definition of recovery is a major methodological problem in ECT studies.

Findings

Prolactin release and improvement

The release of prolactin after the first ECT did not correlate with the extent of eventual improvement in symptoms of depressive illness over a
course of ECT. Nor did the release of prolactin after the first ECT predict accurately the likelihood of recovery after ECT. Simulated ECT also increases plasma prolactin concentration, which suggests that psychological and/or physiological stimuli other than those specific to the induction of cerebral seizure activity lead to the release of prolactin.

Neurophysin release and improvement

The association between release of oxytocin-associated neurophysin after the first ECT and clinical improvement was first found using the RIA of Robinson and later confirmed with the RIA of Legros. A direct comparison between the assays and their association with clinical improvement was not possible because the Robinson RIA is no longer available locally, and it may be that one RIA is a more valid measurement of oxytocin release than the other. The association between the release of the oxytocin-associated neurophysin and clinical improvement was present both in men and women, and in patients free of phenothiazine drugs.

The simplest explanation of the association, and the one which is in line with recent evidence concerning the efficacy of ECT, is that the release of the oxytocin-associated neurophysin is a sensitive measure of electrical stimulation of the mid-brain. This may be related to outcome because the dose of electrical stimulation in excess of seizure threshold is an important influence on the antidepressant efficacy of the induced cerebral seizure. This explanation would also explain why the release of the vasopressin-associated neurophysin is not related to
clinical improvement because the electrophysiological properties of oxytocin- and vasopressin-containing neurones in the posterior pituitary are distinct. The effect of simulated ECT on neurophysin release is not known, but anaesthesia does not increase the release of the oxytocin-associated neurophysin. The stimuli which increase release of the oxytocin-associated neurophysin during ECT are more likely to be specific to the induction of cerebral seizure activity than is the case with prolactin. A second, and more speculative, explanation is that the release of the oxytocin-associated neurophysin occurs at the same time as the release of peptide which has mood-regulating properties (the "neuroendocrine hypothesis" of the mode of action of ECT). No such neurotransmitter or peptide has been identified, although candidates include enkephalins which are co-localized with oxytocin, TRH and oxytocin itself.

Neurophysin release and recovery

The predictive accuracy of hNpII release after the first ECT was not sufficiently great to improve upon available selection criteria based on the assessment of presence of the typical features of depressive illness. The problem remains that about 15% of contemporary depressed patients treated by a course of ECT gain little or no benefit.
Future study

Neurophysin release and clinical improvement

The hypothesis that hNPII release is a sensitive measure of electrical stimulation of the midbrain may be tested in depressed patients treated by ECT. A suitable design would be to compare hNPII release after electrical stimulation just above the seizure threshold with hNPII release after electrical stimulation considerably in excess of seizure threshold. A comparison of the effect of stimulus intensity within the same patients is a design more likely to detect any difference than a comparison between two groups of patients, one treated by stimulation at threshold and one by suprathreshold stimulation. The intensity of electrical stimulation may be varied in two ways, namely, electrical current and the frequency of the electrical pulses. It is important that only the intensity of electrical stimulation is altered and not the waveform. Modern constant current ECT machines allow adjustment both of the electric current and the frequency of stimulation without alteration of the brief-pulse wave.

Oxytocin release after ECT

The hypothesis that ECT induces a rapid and robust increase in the release of oxytocin can be tested if access to an RIA for oxytocin is available.
Neurophysin release and cerebral seizure activity

More sophisticated measures than EEG recording are being developed to study the effects of cerebral seizure activity, for example, SPECT. A testable hypothesis is that the release of the oxytocin-associated neurophysin (or oxytocin itself) is correlated with the altered blood flow observable in limbic or midbrain areas during or after an ECT seizure.

Cerebral seizure activity and clinical improvement

The hypothesis that clinical improvement during a course of ECT is related to the cumulative length of spike-wave cerebral seizure activity is a testable hypothesis. A suitable design will include the EEG recording of each ECT and the clinical assessment of improvement after fixed numbers of treatments. Assessment after fixed numbers of ECT would control for the effect of the number of treatments which has not been done before in studies of the relationship of cerebral seizure activity to clinical improvement. The hypothesis can be tested separately in patients all of whom recover fully after ECT.


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ATTACHED PUBLICATIONS


OESTROGEN-STIMULATED NEUROPHYSIN AND OUTCOME AFTER ELECTROCONVULSIVE THERAPY

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Summary Plasma concentrations of oestrogen-stimulated neurophysin (ESN), prolactin, and growth hormone were measured before and after the first treatment in a course of electroconvulsive therapy (ECT) given to 25 psychiatric patients and during induction of anaesthesia in 9 women undergoing elective cholecystectomy. Prolactin levels rose and growth hormone levels fell during both cholecystectomy and ECT, but ESN levels rose only after ECT. The peak ESN response to ECT was significantly greater (p<0.005) in the 16 depressed patients who recovered than in the 9 who did not. All patients in whom plasma ESN concentration increased by more than 100% satisfactorily recovered from their depressive illness. If a 63% increase in ESN concentration is used to classify all subjects, 12% are misclassified by outcome at 2 months. The extent of the ESN response, but not the prolactin or growth hormone responses, correlated with improvement in symptoms measured by Hamilton Rating Scale for Depression and the Montgomery and Asberg Depression Rating Scale.

Introduction We have sought to relate the endocrine effects of electroconvulsive therapy (ECT) to recovery from depression for two reasons. First, the neurotransmitters implicated in the pathophysiology of depressive illness (serotonin,1 noradrenaline,2 and acetylcholine)3 are also involved in the neural regulation of the hypothalamic/pituitary system.4 The precise extent and timing of hormone release after ECT can provide information about the effects of ECT on central neurotransmitter function in depressed patients. Secondly, the plasma concentrations of some, but not all, pituitary hormones increase rapidly after ECT. We postulated that anaesthesia alone would produce some of these hormone responses5 but that other selective endocrine effects of ECT would be produced only by seizure activity—the therapeutic element of ECT—and that these would be related to its antidepressant action.

Our preliminary studies6 (and unpublished observations) suggested that the selective release of oestrogen-stimulated neurophysin (ESN) after ECT might play such a part. ESN and oxytocin are co-synthesised and released stoichiometrically and, although ESN has no known physiological function, plasma ESN concentrations provide an accurate guide to oxytocin release with the advantages of easier detection and longer half-life.

For ethical reasons, we did not give anaesthesia without ECT to depressed patients but instead compared the endocrine responses to ECT with those in patients undergoing elective cholecystectomy. Prolactin is the hormone most consistently and extensively released in response to ECT.6 Although growth hormone is often released after noxious stimuli7 it is unresponsive to ECT and levels may even fall.8

Patients and Methods

Depressed Patients During the study period (April—August, 1985) 84 patients received ECT at the Royal Edinburgh Hospital; 40 of these patients were assessed. 15 patients were excluded because of serious physical illness, presence of symptoms suggesting organic cerebral disease, or inability to comply with the study or give consent. The sample consisted of 19 women (mean age 47.5 years, range 22—84) and 6 men (mean age 59.7 years, range 50—72). In 11 of the patients a therapeutic dose of an antidepressant drug given for a minimum of 4 weeks had failed to bring about improvement; 17 had previously received courses of ECT and none within the previous 3 months. An indwelling intravenous catheter was inserted about 90 min before ECT. Blood samples (5 ml) were taken 60 min, 30 min, and 2 min before treatment and after electrical stimulation, every 2—5 min to 15 min, then at 30 min, 1 h, 2 h, and 4 h.

A. L. GERBER AND OTHERS: REFERENCES—continued

Clinical Assessment

Diagnoses were made by means of the Research Diagnostic Criteria. The Hamilton Depression Rating Scale and Brief Psychiatric Rating Scale were used to rate the severity of illness before treatment and the extent of eventual recovery. The Montgomery and Asberg Depression Rating Scale was added during the study. Clinical ratings were obtained the day before the first ECT and 7–10 days after the last. All patients continued to receive maintenance doses of oral antidepressants. At 2 months, outcome was assessed by case-note review and was defined as follows.

Good outcome—(14 patients) Hamilton depression rating score <8 at 7–10 days after last ECT, discharged from hospital, returned to usual social activities, remained well with no additional antidepressant treatment.

Good outcome after more ECT—(2 patients) As above, but recurrence of depression during within 10 days of last ECT requiring more ECT.

Poor outcome—(9 patients) Hamilton depression rating score >7 after last ECT, requiring additional oral antidepressants, or remaining in hospital at 2 months, or readmitted to hospital during this period.

All clinical assessments were made without knowledge of the hormonal results.

ECT

ECT was given between 0915 and 0945 h after an overnight fast. Anaesthesia was induced by thiopentone sodium followed by suxamethonium to produce muscle relaxation. No regular anaesthetic premedication was prescribed and no patient received atropine. The choice between unilateral and bilateral placement of electrodes was made by the referring psychiatrist.

Bilateral ECT (11 patients) was given with electrodes in the bitemporal position and unilateral ECT (14 patients) with electrodes in the Lancaster position (temporoparietal). The electrical stimulus at the first treatment was standard; a 'Neurotonic Therapy System' ECT machine delivered 600 mA over 5 s in 2 ms pulses at a frequency of 100 Hz. The duration of a seizure was timed by the observation of clonic-tonic activity in the isolated forearm. A course of ECT consisted of 2–12 (mean 6.9) treatments given with intervals of less than 7 days, as directed by the responsible psychiatrist. When the interval exceeded 7 days, the course of ECT was regarded as complete, although 2 subjects had further treatments beginning 14 and 16 days after the last ECT.

Cholecystectomy Patients

9 women (mean age 44 years, range 23–72) in good general health were studied during elective cholecystectomy. 1.0–1.5 h after atropine 0.6 mg subcutaneously and temazepam 10–20 mg, anaesthesia was induced by thiopentone sodium followed by suxamethonium (as in ECT) and maintained by nitrous oxide and oxygen. Our preliminary study had shown that ECT stimulated ESN release after atropine (0.6 mg) premedication. 3 min after the start of thiopentone induction, the patient was intubated, and after 14–22.5 min a right subcostal incision was made. Blood samples were collected from an indwelling cannula inserted before atropine premedication, 4 min and 1 min before thiopentone, 1 min and 2 min after the start of intubation, and every min for 4 min after abdominal incision.

Hormone Assays

Blood samples were placed immediately into lithium-heparin-coated tubes containing 100 kallikrein-inactivating units of avenol (Bayer UK Ltd) and stored at 4°C. Plasma was separated by centrifugation at 4°C after collection of the last sample and stored at −40°C. Plasma hormone concentrations of ESN, prolactin, and growth hormone were determined by means of the radioimmunoassay kits from the National Institute of Arthritis, Diabetes, and Diseases of the Kidney.

The reference preparation for ESN was that given to the Institute by Dr A. Robinson, University of Pittsburgh. The reference preparation for prolactin was PRL-RP-1 (AFP - 2312C) and that for growth hormone HS2243E. The sensitivities of the assay (90%, B/Bo) were 80 pmol/l for ESN (100 µl sample), 70mU/l for prolactin (50 µl sample), and 1 µmol/l for growth hormone (100 µl sample). The mean coefficients of variation between and within assays of two or three quality controls for each assay were below 10%.

Statistics

Comparisons between groups with good and poor outcomes were made by means of the integrated mean plasma hormone concentration after ECT, expressed as the percentage increase over pre-ECT mean plasma hormone concentration. The extent of recovery was expressed as the percentage improvement in the depression rating scales; because these data were skewed, Spearman's method was used to correlate percentage improvement on each clinical scale with percentage increase in plasma hormone concentration and peak plasma hormone concentration. The hormone responses to cholecystectomy were near normally distributed and were assessed by analysis of variance for repeated measures and Student's paired t-test to locate the timing of significant differences between successive plasma samples.

Results

There were five research diagnostic criteria categories in the sample: major depressive disorder (12 patients), major depressive disorder psychotic subtype (10), probable major depressive disorder psychotic subtype (1), probable major depressive disorder (1), and schizoaffective disorder depressed type (1). In addition to ECT, 12 patients also received an antidepressant drug, 5 patients a neuroleptic drug, 2 patients lithium carbonate, and 5 patients more than one psychotropic drug. There was no relation between the concomitant use of antidepressant medication at the time of the first ECT and either the percentage increase in ESN or subsequent outcome. The clinical ratings before and after ECT are given in the table. Good and bad outcome groups did not differ significantly in age, initial severity, number of previous episodes, or treatment laterality.

Fig 1 shows the prolactin, ESN, and growth hormone responses to ECT in the good (16 patients) and poor (9 patients) outcome groups. Prolactin levels in both groups peaked at 12.5 min; although the increase was about twice as great in the good outcome group, this difference was not significant. ESN peaked at 2.5 min, when the increase in the good outcome group was approximately 30% (p<0.05) than that in the poor outcome group. There were no significant correlations between any of the hormonal responses and seizure duration.

<table>
<thead>
<tr>
<th>Rating scale</th>
<th>Before ECT</th>
<th>After ECT</th>
<th>% improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamilton depression</td>
<td>23.0 ± 0.9 (15–31)</td>
<td>5.1 ± 0.7 (0–13)</td>
<td>77 ± 3.7 (19–100)</td>
</tr>
<tr>
<td>Brief psychiatric</td>
<td>19.6 ± 1.3 (8–31)</td>
<td>5.2 ± 0.7 (1–13)</td>
<td>71 ± 3.5 (25–93)</td>
</tr>
<tr>
<td>Montgomery &amp; Asberg depression (n = 17)</td>
<td>31.2 ± 1.7 (14–46)</td>
<td>8.6 ± 1.7 (0–22)</td>
<td>72 ± 5.1 (19–100)</td>
</tr>
</tbody>
</table>
concentrations between patients receiving unilateral and bilateral treatment.

Plasma prolactin concentrations increased significantly over time (0.51±0.10 IU/l to 2.10±0.61 IU/l; p<0.001) during cholecystectomy, growth hormone levels fell significantly (3.4±0.7 mIU/l to 2.9±0.18 mU/l; p<0.01), and there was no change in ESN (196±17 pmol/l to 204±22 pmol/l). The increase in prolactin was significant (p<0.05) 2 min after intubation and from 1 min to 4 min after subcostal incision.

The percentage increase in ESN correlated with percentage improvement in Hamilton Depression Rating score (r=0.49, p<0.02; peak response r=0.43, p<0.05) and in Montgomery and Asberg Depression Rating (r=0.60, p<0.02; peak response, r=0.62, p<0.01). There was no significant correlation with percentage improvement in Brief Psychiatric Rating score. There were no significant correlations between the prolactin or growth hormone responses to ECT and clinical outcome.

**Discussion**

Our findings support our hypothesis that the ESN response to the first ECT is related to the extent of recovery from depression. We have shown that a selective hormonal effect of ECT can be related to its antidepressant action.

The release of prolactin and growth hormone is influenced by age, sex, reproductive status, and the use of psychotropic drugs. Although these factors may have confounded a possible relation between hormone release after ECT and clinical outcome, it is more likely that prolactin and growth hormone responses are not specific to ECT and are unrelated to its antidepressant action. Psychotropic drugs administered at the time of the first ECT probably do not affect the relation between peak ESN response and subsequent outcome, since the use of such drugs could not be related either to ESN response or to subsequent outcome. The similar falls in growth hormone after ECT and during cholecystectomy suggest that anesthesia produces this effect, a finding consistent with a previous report.

There are several possible explanations for our findings. First, the ESN response to ECT may be a measure of electrical stimulation and/or seizure activity of magnocellular neurons. The release of oxytocin, and by inference ESN, is a direct function of the number of action potentials entering the posterior pituitary from the magnocellular nuclei of the hypothalamus. In addition to having effects elsewhere in brain, ECT may, therefore, be a potent specific stimulus of ESN/oxytocin release. The ESN response to ECT thus might be a measure of electrical activity that also produces the antidepressant effect. This explanation is not, however, supported by the finding that the ESN response was unrelated to seizure duration or electrode placement.

A second possibility is that through ESN/oxytocin release, ECT may modify the effects of neurotransmitters concerned with the regulation of mood. These posterior pituitary peptides are found at sites in the central nervous system without an obvious endocrine function (eg, limbic system and spinal cord), but it is by no means clear how the enhanced release of ESN/
oxytocin might promote recovery from depression.

A third, and we believe more likely, possibility is that the increased release of ESN reveals an underlying disturbance of the neural control of oxytocin release in a subgroup of depressed patients. This abnormality may lie elsewhere in brain and may be modified by ECT. We have found substantial individual variation in the ESN response to first ECT that was consistently reproduced at the second ECT; this finding suggested that ECT produced exactly the same effect on ESN/oxytocin release on each occasion. The neurobiology of ESN/oxytocin is incompletely understood; release involves noradrenaline, acetylcholine, and dopamine, but probably neither serotonin nor gamma-aminobutyric acid. Atropine premedication in our earlier study did not modify ESN release after ECT, suggesting that cholinergic pathways are probably not involved in this response. Dopaminergic activation may bring about ESN release after ECT, but this possibility seems unlikely because dopaminergic activity would tend to reduce rather than increase prolactin release.

Neurochemical and behavioural studies have, however, shown that electroconvulsive shocks produce major changes in noradrenergic function by reducing β-adrenoceptor numbers and increasing noradrenaline synthesis and turnover. Effects of electroconvulsive shocks on serotonergic function may depend upon the integrity of noradrenergic transmission. Electroconvulsive shocks, like all effective antidepressant treatment, modify noradrenergic and serotonergic neurotransmission. Although noradrenergic neurons are important in the regulation of ESN/oxytocin release, serotonergic neurons do not appear to be involved. Thus we infer that the greater ESN response to ECT in patients who improve is likely to reflect abnormalities in noradrenergic neurotransmission. Our findings may prove useful in the prediction of response to ECT and thus be relevant to the biological subclassification of depressive illnesses.

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Hypothesis

MEMBRANE STABILISING ACTIVITY: A MAJOR CAUSE OF FATAL POISONING

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Summary

Many of the agents held responsible for fatal poisoning in England and Wales—particularly dextropropoxyphene, tricyclic antidepressants, β-adrenoergic antagonists, and chlorpromazine—possess membrane stabilising activity (MSA). This pharmacological property, although regarded as being of little importance in therapeutic use, may be responsible for death in more than 30% of fatal poisonings. Awareness of this possibility may lead to greater care in the prescribing of drugs with this property, to the development of safer alternatives, and to more rational therapy of the poisoned patient.

INTRODUCTION

How drugs and poisons exert their acute, lethal effects is not always known and is seldom predictable from their intended pharmacological effects (table I). Several agents which cause fatal poisoning in man have membrane stabilising activity—eg, neuroleptic agents, opioids, barbiturates, tricyclic antidepressants, and β-adrenoergic antagonists. Membrane stabilising activity (local anaesthetic or quinidine-like activity, MSA) is the non-specific interaction that occurs between membrane lipid bilayers and many lipophilic drugs and chemicals; this interaction inhibits the fast inward passive Na+ current (depolarisation) and thus the action potential in excitable cells. Although this property may be important in the pharmacological action of tranquillisers and anaesthetic agents and some antiarrhythmic drugs, it is not thought to be relevant to the actions of most other drugs when they are taken in therapeutic doses. However, we suspected that when overdoses of these drugs are taken, the effect of their MSA may be fatal, so we have reviewed the evidence for the importance of MSA in acute fatal poisoning.


Treatment Outcome, Seizure Duration, and the Neurophysin Response to ECT

Allan I. F. Scott, Lawrence J. Whalley, and Jean-Jacques Legros

Serum concentrations of immunoreactive neurophysin (IRN) and vasopressin-associated neurophysin (hNpI) were measured before and after the first treatment in a course of electroencephalographically monitored electroconvulsive therapy (ECT) given to 19 depressed patients. The difference (DIFF) between the serum concentrations of IRN and hNpI is equivalent to the concentration of oxytocin-associated neurophysin. Before ECT the six patients who had a good outcome at 2 months after the course of ECT had a mean serum IRN concentration one-half ($p < 0.05$) and a mean serum DIFF concentration one-third ($p < 0.05$) that of the 13 patients who had a poor outcome. The increase in serum DIFF concentration (but not IRN or hNpI) after the first ECT correlated with the improvement on the Hamilton Rating Scale for Depression ($r = -0.73, p < 0.005$) and the Montgomery and Asberg Depression Rating Scale ($r = -0.49, p < 0.05$). The peak percentage increase in serum DIFF concentrations after ECT was 4 times greater ($p < 0.001$) in the good outcome group than in the poor outcome group. None of the neurophysin responses to ECT correlated with electroencephalogram-measured seizure duration.

Introduction

Our previous work has shown that there are rapid increases in the plasma concentrations of the neurophysins, prolactin, and adrenocorticotropin (ACTH), smaller increases in plasma luteinizing hormone and cortisol, but no change in plasma thyrotropin-releasing hormone or thyrotropin after electroconvulsive therapy (ECT) (Whalley et al. 1982, 1987). We later studied a series of 25 depressed patients and examined only those hormones that we had tentatively associated with subsequent improvement (Scott et al. 1986) and identified a positive relationship between the release of oxytocin-associated neurophysin (the estrogen-stimulated neurophysin) after the first ECT and the extent of recovery from depressive illness.

Seizure activity is the essential therapeutic component of ECT (Kendell 1981). Thus, it is possible that our previous studies demonstrated a relationship between a sensitive hormonal measure of seizure activity and subsequent outcome. Although such a finding would be of interest, it would not provide a satisfactory basis for further studies to elucidate...
the mode of action of ECT. The first aim of this study was to test the hypothesis that
the oxytocin-associated neurophysin response to ECT was a marker of seizure activity
[measured reliably by a multichannel electroencephalogram (EEG)].

The second aim of the study was to replicate our previous findings using a different
radioimmunoassay (RIA) for measuring neurophysins. The posterior pituitary hormones
oxytocin and vasopressin are synthesized as parts of much larger precursor molecules,
or preprohormones (Ivell et al. 1983). Release of oxytocin or vasopressin is accompanied
by the simultaneous release of their respective neurophysins. Measurement of neurophysins
in peripheral blood provides a good guide to the discharge of oxytocin and vasopressin
from the posterior pituitary with the advantage that the neurophysins have a longer half-life. It would also have been interesting to measure oxytocin and vasopressin directly,
but at the beginning of the study, we did not have access to reliable assays of oxytocin
and vasopressin.

RIA methods for the neurophysins have been developed separately in laboratories in
North America and Europe. At present, there is no international standard, and it is possible
that results obtained in one laboratory are not directly comparable with another. The RIA
for measuring immunoreactive neurophysins (IRN) was first described by Legros et al.
(1969), who later established a method to detect the vasopressin-associated neurophysin.
The human vasopressin-associated neurophysin that migrates to the anode in electrophoresis is therefore named neurophysin-I (hNP1) (Legros and Louis 1973). Working separately,
a group in Pittsburg (Robinson 1975) followed with methods for a neurophysin that increased in plasma in response to cigarette smoking (nicotinic-stimulated neurophysin, which is equivalent to the vasopressin-associated neurophysin) and a neurophysin that increased in plasma in response to estrogen (the estrogen-stimulated neurophysin, which is equivalent to the oxytocin-associated neurophysin). IRN is equivalent to the total amount of oxytocin- and vasopressin-associated neurophysins in peripheral blood (Legros 1975). In our previous study (Scott et al. 1986), we used RIA materials generously
donated to the pituitary hormone program of NIADDK by Dr. Robinson. In the present
study, we sought to test the hypothesis that treatment outcome is associated with the
neurophysin response to ECT as measured by the alternative RIA developed by Legros.

Methods

Depressed Patients

The study protocol was approved by the Psychiatry and Clinical Psychology Ethics
Research Sub-Committee of the Lothian Health Board. Nineteen patients admitted to the
Royal Edinburgh Hospital for inpatient treatment of unipolar depressive illness were
studied. The patients had not received ECT within 6 months, had no physical illness or
symptoms suggestive of organic cerebral disease, and were able to give informed consent
and to comply with study procedures. None of the patients were hypertensive or obese.
There were 16 women and 3 men (mean age 50.0 years, SE ± 3.7 years), and all met
Research Diagnostic Criteria (RDC) (Spitzer et al. 1978) for probable (n = 1) or definite
(n = 18) major depressive disorder. At the first ECT, none of the subjects was drug-
free: 14 received regular oral antidepressants (2 in combination with a benzodiazepine,
4 with a phenothiazine), 4 received a phenothiazine alone, and 1 a benzodiazepine alone.
None of the women was taking an oral contraceptive pill. Seven of the patients smoked
cigarettes. Severity of depression was rated on the Hamilton Rating Scale for Depression (HRSD) (Hamilton 1960) and the Montgomery and Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979).

**Assessment of Outcome**

The duration of benefit of ECT is uncertain (Kendell 1981), and thus, there is no general agreement about the timing of assessment after ECT. A common time for relapse is about 2 weeks after the last ECT. For these reasons, we chose to use two measures of outcome. Before ECT, all patients were assessed on the clinical ratings the day before the first ECT. Outcome was assessed 7–10 days and 2 months after the last ECT. Good outcome at 7–10 days after ECT was defined as an HRSD score of less than 8. All patients received therapeutic doses of antidepressant drugs as continuation therapy. Outcome at 2 months was classified as follows:

- **Good outcome** (n = 6): HRSD < 8, 7–10 days after the last ECT; discharge from hospital, return to usual social activities, and remains well with only continuation doses of antidepressant drugs.

- **Poor outcome** (n = 13): HRSD score > 7, 7–10 days after the last ECT or relapse of depression requiring drug treatment over and above continuation antidepressants or readmission to hospital.

All clinical assessments were made without knowledge of the hormone results.

**ECT**

ECT was given between 9:00 and 10:00 AM after an overnight fast. Anesthesia was induced by thiopentone sodium, followed by suxamethonium. No regular premedication was given, and no subject received atropine. Bilateral ECT (10 patients) and unilateral ECT (9 patients) were prescribed by the supervising clinician. Electrical stimulus at the first treatment was standard: an Ectron CCX Series 3 ECT machine delivered 850 mA over 5 sec in 1.5-msec pulses at a frequency of 45 Hz. The duration and extent of the induced seizure was monitored by 6 channels of an SLE 100P portable EEG. The EEG recording was read by two independent observers, and the duration of seizure activity was taken as the mean of their estimates.

**Blood Sampling**

An indwelling intravenous catheter was inserted about 90 min before ECT. Cigarette smoking enhances the release of vasopressin-associated neurophysin, but usually does not affect the release of oxytocin-associated neurophysin. Serum concentrations of neurophysins return to normal 20 min after smoking stops (North et al. 1980). Patients may have been smoking on the ward before ECT, but no patient smoked within 15 min of the first blood sample. Blood samples (5 ml) were taken 30 min, 15 min, and 1 min before treatment and after electrical stimulation at 2.5, 5, 7.5, 10, 12.5, 15, 30, and 60 min. Blood samples were placed immediately in plain tubes and stored at 4°C. Serum was separated by centrifugation and samples stored at −20°C.
Hormone Assays

Serum hormone concentrations were determined in the Neuroendocrinology Section at the University of Liege. IRN were measured using the original RIA described previously (Legros et al. 1969); vasopressin–neurophysin (hNpI) was assayed using a recently developed RIA available only in this laboratory.

In summary, hNpI was used as standard and labeled. The labeling of hNpI was realized as for the IRN RIA, the specific activity being 225 ± 25 μCi/μg. Anti-hNpI antiserum was used at the initial dilution of 1/10,000. Separation of free from bound hormones was achieved by double-antibody techniques. At this dilution, ±30% of the tracer (±9,000 cpm) was bound, the limit of detection being 0.02 ng/tube, and the sensitivity (50% inhibition binding) being 0.2 ng/tube. The volume of known or unknown samples was usually 100 μl. Cross-reaction of oxytocin neurophysin (hNpII) was detectable at 0.01 level; no cross-reactivity was detected using synthetic nonapeptide (oxytocin or vasopressin) or purified extracted human anticyphysyal hormone.

Intraassay variability was 6.5% and interassay variability was 10.7%; all the samples of one individual were assayed in the same run.

Statistics

The differences in clinical variables between outcome groups were assessed using Student’s t-test and Fisher’s exact probability test. The neurophysin responses to ECT were skewed and thus assessed, after square-root transformation, by Analysis of Variance for repeated measures (Winer 1971). Student’s t-test was used post hoc to locate the timing of significant differences in hormone response between outcome groups. The extent of each hormonal response to ECT was expressed as the percentage increase in integrated mean serum hormone concentration over mean baseline concentration. The extent of recovery from depression was expressed as the absolute improvement in the depression rating scales. Pearson’s method was used to correlate absolute improvement on each clinical scale with percentage increase in serum hormone concentration and duration of seizure activity. All probabilities are expressed as two-tailed p-values.

Results

Initial assessment of outcome at 7–10 days after ECT showed that 7 patients met the criteria for good outcome. Assessment at 2 months after the last ECT revealed that one of the patients who had had a good outcome 7–10 days after ECT relapsed a week later and required readmission to hospital. The clinical details of the patients are shown by outcome group at 2 months after ECT (Table 1). There were no significant differences between the two groups before ECT in age, sex, RDC category, severity of depression, or drug treatment. A greater proportion of the good outcome group received bilateral ECT (4 of 6 patients versus 6 of 13 patients), but this was not statistically significant (Fisher’s exact test, p = 0.63). There was no significant difference in percentage improvement on the HRSD score between those patients treated with unilateral and bilateral ECT.

Figure 1 shows the serum neurophysin concentrations before and after the first treatment of the course of ECT by outcome group. The results for total immunoreactive neurophysin (IRN), the vasopressin-associated neurophysin (hNpI), and the difference (DIFF) between the two (equivalent to the oxytocin-associated neurophysin) are shown separately. Before
Neurophysins and ECT

Table 1. Clinical Details by Clinical Outcome 2 Months after Last ECT

<table>
<thead>
<tr>
<th></th>
<th>Good (n = 6)</th>
<th>Poor (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>1M/5F</td>
<td>2M/11F</td>
</tr>
<tr>
<td>Age ± se</td>
<td>54 ± 5.0</td>
<td>48 ± 4.8</td>
</tr>
<tr>
<td>RDC category*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMDD</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>DMDD</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>DMDD-P</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Initial HRSD ± se</td>
<td>21.3 ± 2.3</td>
<td>23.9 ± 1.5</td>
</tr>
<tr>
<td>Initial MADRS ± se</td>
<td>30.8 ± 3.3</td>
<td>35.6 ± 1.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug therapy (first ECT)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepine (BZd)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Phenothiazine (PZ)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Antidepressant (AD)</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>AD + BZD</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>AD + PZ</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>ECT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Bilateral</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Final HRSD ± se</td>
<td>3.0 ± 1.0</td>
<td>14.0 ± 1.9*</td>
</tr>
<tr>
<td>Final MADRS ± se</td>
<td>5.0 ± 2.8</td>
<td>17.6 ± 3.3*</td>
</tr>
<tr>
<td>Percentage improvement HRSD ± se</td>
<td>85.1 ± 5.3*</td>
<td>38.2 ± 6.1*</td>
</tr>
</tbody>
</table>

*RDC categories: PMDD, probable major depressive disorder; DMDD, definite major depressive disorder; DMDD-P, definite major depressive disorder, psychotic subtype.

^Significantly (p < 0.01) greater than score in good outcome group.

^Significantly (p < 0.05) greater than score in good outcome group.

^Significantly (p < 0.001) greater than score in poor outcome group.

ECT, serum concentrations of IRN and DIFF were greater in the poor outcome group than in the good outcome group at each of the three sampling points. There was one woman in the poor outcome group in whom serum DIFF was undetectable before ECT, and she was excluded from further calculations involving baseline DIFF. Table 2 shows that the mean baseline serum IRN concentration was twice as great in the poor outcome as in the good outcome group (p < 0.05). The mean baseline serum DIFF concentration was 3 times greater in the poor outcome group than in the good outcome group (p < 0.05). Although there was a significant difference between the outcome groups in mean baseline DIFF concentration, there was a considerable overlap between the groups. Mean baseline serum DIFF concentration was not useful in the prediction of clinical outcome. There were no statistically significant differences between outcome groups in baseline serum hNpI concentration. There were no correlations between mean baseline neurophysin concentrations and the severity of depression measured on the HRSD or MADRS.

One factor contributing to the baseline differences in serum IRN and DIFF concentration between outcome groups may be the different phenothiazine exposures in the two groups. The mean baseline serum IRN and DIFF concentrations were significantly lower in those taking phenothiazines. In the 11 neuroleptic-free patients, mean baseline IRN concentration was 0.88 ± 0.11 ng/ml, but in the 8 patients taking phenothiazines, mean baseline IRN concentration was only 0.41 ± 0.09 ng/ml (p < 0.01). Mean baseline DIFF concentration was three times greater in neuroleptic-free patients than in those
Figure 1. Serum neurophysin concentrations (mean ± standard error) after first treatment of a course of ECT by clinical outcome 2 months after last ECT. *Concentration in poor outcome group (n = 13) significantly (p < 0.05) greater than concentration in the good outcome group (n = 6).

patients taking phenothiazines (0.63 ± 0.10 ng/ml versus 0.22 ± 0.07 ng/ml, p < 0.01). A greater proportion of the patients in the good outcome group were receiving phenothiazines compared with patients in the poor outcome group (4 of 6 patients versus 4 of 13; Fisher's exact test, p < 0.32). There was no difference in serum neurophysin concentrations between those patients taking and not taking tricyclic antidepressants, and thus, these drugs did not affect serum neurophysin concentrations.
Table 2. Baseline Neurophysin Concentrations (ng/ml) by Clinical Outcome
2 Months after Last ECT

<table>
<thead>
<tr>
<th>Neurophysin</th>
<th>Poor (n = 15)</th>
<th>Good (n = 6)</th>
<th>Poor (n = 9)</th>
<th>Good (n = 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRN</td>
<td>0.81 ± 0.12</td>
<td>0.39 ± 0.34&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.98 ± 0.11</td>
<td>0.38 ± 0.05&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>hNpI</td>
<td>0.27 ± 0.04</td>
<td>0.21 ± 0.01</td>
<td>0.26 ± 0.05</td>
<td>0.20 ± 0.00</td>
</tr>
<tr>
<td>DIFF</td>
<td>0.62 ± 0.10&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.20 ± 0.03&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.73 ± 0.09</td>
<td>0.20 ± 0.07&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Values are means ± SEM.

<sup>a</sup>n = 12. In one patient, DIFF was undetectable before ECT.

<sup>b</sup>Significantly (p < 0.05) lower concentration than in the corresponding poor outcome group.

Table 2 shows that when the analysis of baseline neurophysin concentrations is restricted to those patients who are free of neuroleptic drugs, those patients who have a good outcome 2 months after ECT (n = 2) have significantly lower concentrations of both IRN and DIFF than those patients who had a poor outcome 2 months after ECT (n = 9).

Serum neurophysin concentrations after ECT were analyzed by Analysis of Variance for repeated measures after square-root transformation. There were highly significant effects of time for all three hormones (IRN: F = 73.6, df 8, p < 0.001; hNpI: F = 40.0, df 8, p < 0.001; DIFF: F = 44.5, df 8, p < 0.001). In addition, there were significant effects of a group-time interaction for IRN (F = 2.1, df 8, p < 0.05) and serum DIFF concentration (F = 2.4, df 8, p < 0.02). The increases in serum neurophysin concentrations were expressed as the percentage increases in integrated mean serum hormone concentration over mean baseline concentration. The extent of the increase in serum DIFF concentration in the total sample correlated significantly both with absolute improvement on the HRSD (r = −0.73, p < 0.005) and the absolute improvement on the MADRS (r = −0.49, p < 0.05). There were no significant correlations between the extent of the increase in either serum concentrations of IRN or hNpI and the degree of clinical improvement. In view of the confounding effects of neuroleptic drugs on baseline serum DIFF concentration, we repeated these correlations for the 11 patients who were free of neuroleptic drugs. The only significant correlations were between the extent of the increase in serum DIFF concentration and absolute improvement on the HRSD (r = −0.74, p < 0.01) and absolute improvement on the MADRS (r = −0.68, p < 0.05).

There were no significant correlations between the extent of the increase in serum neurophysin concentrations and EEG-measured seizure duration. The correlations (r) with total seizure length were: IRN, r = 0.00, p = 0.99; hNpI, r = 0.16, p = 0.52; and DIFF, r = 0.11, p = 0.67. There were no significant differences in the extent of the increase in serum neurophysin concentrations between unilateral (n = 9) and bilateral (n = 10) ECT.

Figure 2 shows the relationship between the peak increase in serum DIFF concentration and clinical outcome 2 months after the last ECT of a course. The extent of the peak increase in serum DIFF concentration is expressed as peak percentage increase over mean baseline. The mean peak percentage increase in the good outcome group is four times
that of the peak percentage increase in the poor outcome group (837 ± 110% versus 202 ± 51%, p < 0.001).

Mean baseline serum DIFF concentration will have a considerable influence on the peak percentage increase. Analysis of Variance of peak percentage increase in serum DIFF concentration was carried out with outcome as a main factor and mean baseline serum DIFF concentration as a covariate. The only statistically significant F-value was for mean baseline (F = 5.39, df 1, p = 0.05). However, mean baseline serum DIFF concentration was not correlated with the extent of improvement on HRSD or MADRS.

There is little overlap between the values of peak percentage increase in serum DIFF concentration in the good and poor outcome groups. If a 500% increase in serum DIFF concentration had been used as a cutoff point to define good and poor outcome groups, then 17 of the 19 patients (89%) would have been classified correctly by outcome at 2 months. (In one patient, DIFF was undetectable before ECT and a peak increase could not be calculated.) The differences in peak percentage increase in serum DIFF between the good and poor outcome groups at 2 months were most marked for men and postmenopausal women. As the release of oxytocin-associated neurophysin is enhanced by the administration of estrogen (Legros and Grau 1973), it may be that the presumed higher plasma concentration of estrogen in the premenopausal women was a confounding factor. However, we did not measure plasma estrogen concentrations. When patients who received neuroleptic drugs at the time of the first ECT were excluded from Figure 2, a similar pattern was still apparent. The two patients who had a good outcome both had
increases greater than 500%, and all 9 patients with a poor outcome had percentage increases below 500%.

Discussion

These findings support our original hypothesis that the extent of the increase in serum concentration of the oxytocin-associated neurophysin after the first ECT is related to the extent of recovery from depression after ECT. Moreover, we have confirmed this association using an alternative assay for the neurophysins in an independent laboratory. There was no support for the hypothesis that the neurophysin response to ECT is a correlate of seizure duration.

An unexpected finding (in these 19 unipolar depressed patients) was that the baseline serum IRN concentration was about half the average value for age- and sex-matched controls. The average serum IRN concentration for healthy men aged 50–60 years is 1.60 ± 0.7 ng/ml and for women is 1.69 ± 0.18 ng/ml (Legros 1975). The mean baseline serum IRN concentration in the poor outcome group (n = 13) was 0.81 ± 0.12 ng/ml, and the mean baseline serum IRN concentration in the good outcome group (n = 6) was 0.39 ± 0.05 ng/ml. This is the first time that unipolar depressive illness has been associated with low serum IRN concentrations. Legros et al. (1983) have reported normal concentrations of hNpII in the cerebrospinal fluid of unipolar depressed patients when compared with a control group of neurological patients. Moreover, the mean baseline serum concentrations of IRN and DIFF were significantly greater in the poor outcome group than in the good outcome group; however, there was no statistically significant difference between outcome groups in baseline serum hNpI concentrations.

Swartz (1986) has pointed out that the intake of neuroleptic drugs may have confounding effects on the relationship between the release of neurophysins and clinical outcome after ECT. Chlorpromazine at a daily dose of 100 mg has been shown to inhibit the stimulatory action of ethinyl estradiol on the release of IRN (Legros et al. 1975). Although there was a difference in baseline serum neurophysin concentration between outcome groups in those patients who were free of neuroleptic drugs (n = 11), this finding must be treated cautiously in view of the small number of patients. In those patients who had a good outcome 2 months after the last ECT, the baseline serum DIFF concentration was less than one-third that of those patients who had a poor outcome after the last ECT.

The duration of benefit of ECT is uncertain (Kendell 1981). Thus, there is no general agreement about the timing of assessments of outcome after ECT. Recent studies suggest that less than a third of patients remain well after 6 months (Coryell and Zimmerman 1983; Lipman et al. 1986; Katona et al. 1987). The results of the present study prompted us to reexamine the data from our earlier study of 25 depressed patients who were treated with ECT (Scott et al. 1986). Only when outcome was assessed at 2 months was there a difference in baseline serum oxytocin-associated neurophysin concentration between the patients with good and bad outcome. Patients with a good outcome 2 months after ECT (n = 16) had a mean baseline serum oxytocin-associated neurophysin concentration two-thirds that of those patients (n = 9) who had a poor outcome 2 months after ECT (107 pmol/liter versus 151 pmol/liter, p < 0.01).

In our previous study, we suggested three possible explanations of our findings. Our first suggestion was that the oxytocin-related neurophysin response to ECT was a sensitive measure of seizure duration, but this is not supported by our present findings. Our second
explanation concerned the control of the release of oxytocin and its associated neurophysin. Siever and Davis (1985) hypothesized that depressive illness may be understood as a failure of regulation of neurotransmitter systems (the "dysregulation hypothesis of depressive illness") rather than simple increases or decreases in their activity. Furthermore, they propose that specific stimuli may probe the regulation of neuroendocrine systems and that effective treatments restore efficient function. We have found that in a subgroup of depressed patients, there is a marked release of the oxytocin-associated neurophysin after ECT and that this subgroup of depressed patients recover after ECT. In terms of the dysregulation hypothesis, ECT acts as a probe, and the increased release of the oxytocin-associated neurophysin after ECT reveals a dysregulation in the neural control of neurophysin release. An implication of the model is that the dysregulation of neurophysin release should be rectified in the subgroup of patients who respond to ECT. Previously, we have shown that the release of the oxytocin-associated neurophysin diminishes over a course of ECT (Whalley et al. 1987), but we do not know if this diminution in release is related to recovery. Our third explanation was that oxytocin or its associated neurophysin had direct behavioral effects on depressed patients. Although it has been noted that many peptide hormones have behavioral effects in addition to their endocrine effects (Nemeroff and Prange 1978), we regarded this explanation as more speculative, as there were no data on the behavioral effects of oxytocin in depressed patients. We would like to update these explanations, drawing on recent data on the wider biological role of oxytocin.

Oxytocin-containing neurons extend to several extrahypothalamic areas of the central nervous system (Buijs 1983). In addition to its role in milk ejection (Lincoln and Paisley 1982) and parturition (Fuchs et al. 1983), oxytocin is released in response to neurogenic or "emotional" stress (Gibbs 1986). Carter and Lightman (1987) reported that the oxytocin response to the stress of immobilization was different in strains of rat selected for emotional reactivity. The authors argued that because oxytocin is released preferentially in response to neurogenic stress and its release is related to emotional reactivity, then the oxytocin response is uniquely applicable as a neuroendocrine measure of emotional state. If these arguments are confirmed (and animal data can be extrapolated to human beings), it could be concluded that the subgroup of depressed patients who respond to ECT can be identified by the oxytocin response to stress.

Oxytocin contributes to the regulation of the hypothalamic–hypophyseal–adrenocortical axis during stress (Gibbs 1986). Oxytocin stimulates ACTH release in animals, but in humans, it inhibits ACTH release. In this way, oxytocin modulates the action of corticotrophin-releasing factor (CRF) during certain types of stress. In recent years, there has been considerable interest in the increased activity of the hypothalamic–pituitary axis in depressive illness. Gold et al. (1984) have suggested that depressive illness may be associated with hypersecretion of CRF; CRF may stimulate not only the pituitary–adrenal axis, but may also influence several aspects of brain function to produce depressive symptoms. If depressive symptoms are produced by CRF, then oxytocin may relieve symptoms by modulating the biological effects of CRF.

Oxytocin may also have direct effects on depressive symptoms by its effects either on learning or memory. In animals, oxytocin facilitates the extinction of conditioned behaviors (Kovacs and Telegedy 1982) and, in humans, impairs learning in healthy volunteers (Fehm-Wolfsdorf et al. 1984; Geenen et al. 1988). Anseaux et al. (1987) have argued that oxytocin's amnesic properties may facilitate the extinction of maladaptive behavior. They reported the effects of intranasal oxytocin in a patient suffering from obsessive-
compulsive disorder; initially, there was a reduction in anxiety and compulsive thoughts, but later, the patient complained of marked memory disturbances and developed delusions of persecution. Although there are still no data on the behavioral effects of oxytocin in depressed patients, oxytocin may directly alleviate depressive symptoms either by its modulation of CRF activity or learning.

In this article, we have sought to generate hypotheses that may be tested in depressed patients and that may advance our understanding of the nature of the association between the neurophysins response and recovery period. The neurophysin response to ECT may reveal an underlying dysregulation of the neural control of oxytocin release in a subgroup of depressed patients who respond to ECT. Further longitudinal studies of depressed patients over a course of ECT are required to test this hypothesis. If the hypothesis is supported, the neurophysin response will be modified over the course of treatment in those patients who recover. Direct measurement of serum oxytocin concentrations after ECT would be of considerable interest; however, concomitant measurement of both oxytocin and its associated neurophysin may only be practicable at a few sampling points, as blood samples in excess of 12 ml are required. A further hypothesis is that oxytocin itself relieves depression either by its modulation of the activity of CRF or by its effects on learning. Oxytocin is now available as an intranasal preparation, but an alternative strategy would be to manipulate the release of oxytocin and its associated neurophysin. The most potent stimulus of oxytocin release that can be used in a controllable fashion is ECT itself; however, the administration of estrogen produces a modest increase in the synthesis and release of the oxytocin-associated neurophysin (Legros and Grau 1973). A testable hypothesis is that administered estrogen augments the antidepressant efficacy of ECT.

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References


Which Depressed Patients will Respond to Electroconvulsive Therapy?  
The Search for Biological Predictors of Recovery  

ALLAN I. F. SCOTT  

A small yet significant minority of contemporary patients with endogenous depressive illness who are treated with electroconvulsive therapy (ECT) gain little or no benefit. It is argued that the use of clinical features alone may not improve the ability to predict outcome after ECT. Many biological measures have been used to attempt to identify depressed patients for whom ECT would be an effective treatment, but none has yet been shown to be superior to clinical predictors. Depressed patients show a wide range of physiological responses to the first treatment of a course of ECT. Of these physiological responses, estimations of seizure threshold and of the release of posterior pituitary peptides merit further investigation as putative predictors of recovery.

The best guide to the likelihood of recovery from depressive illness after electroconvulsive therapy (ECT) is the diagnosis itself. The classical symptoms of endogenous depressive illness predict a good response to ECT, while those of neurotic depression do not (Fink, 1979; Kendell, 1981; Hamilton, 1986). The well-known Medical Research Council (1965) investigation of treatments for depressive illness showed that 84% of patients suffering from endogenous depression improved with ECT. A small minority of patients with classical endogenous depressive illness, however, receive ECT with little or no benefit. Thus, there have been many attempts to identify biological measures which may select endogenously depressed patients who will respond well to ECT.

There are other important reasons for this interest. Firstly, there has never been agreement about the clinical boundaries of endogenous depressive illness. Secondly, Abrams (1982) has argued that there is now so little clinical variability among depressed patients who receive ECT that the prediction of outcome based on clinical features alone may not be feasible. Thirdly, the identification of biological predictors of recovery after ECT would provide clues about the mode of action of this controversial treatment. A fourth contemporary hope is that the identification of the characteristics of depressed patients who respond rapidly to ECT may form the basis of a subclassification of depressive illness. This subclassification might in turn advance understanding of the aetiology of certain types of depressive illness. This everyday clinical problem is thus complicated by crucial uncertainties about classification in psychiatric illness and its answer may have important implications for research into the aetiology of depressive illness.

What are we trying to predict?  
The prediction of treatment response is a continual concern for psychiatrists and their patients. Biological measures may help in a number of ways (Albala et al., 1984). It may be possible to identify depressed patients for whom ECT would be the most effective treatment; or to monitor the process of recovery and determine the optimal end-point for a course of ECT; or to detect, among patients who have successfully completed a course of ECT, those who are at high risk of relapse and in need of continuing supervision or vigorous continuation therapy. This review will be concerned chiefly with attempts to identify depressed patients for whom ECT would be an effective treatment.

Biological measures as potential predictors of outcome  
Early studies concentrated on biological measures made before patients received any ECT (Table I). The simplest strategy was to investigate a resting physiological measure such as the concentration of a substance in blood, or an electroencephalogram (EEG). A later strategy was to study the physiological effects of administered drugs. Funkenstein’s test studied the effects of administered adrenaline and metacholine on blood pressure, and the sedation threshold test measured the effects of sodium amytal.
on the EEG. Recent studies have used administered drugs or hormones in neuroendocrine challenge tests. Although depressed patients who are treated by ECT are highly selected and share many clinical features, they show a variety of behavioural and physiological responses to ECT (Fink, 1979). The search for predictors of outcome may be more rewarding if based on reaction to the treatment. The clinical response to the first few treatments is a good guide to the likelihood of recovery (Price et al, 1978; Zorunski et al, 1986), and to be of value as a predictor, the measure employed must be informative after the first or second application of ECT. Table II lists physiological measures of the response to the first treatment of a course of ECT which have been investigated as potential predictors of outcome.

Some methodological problems
Early attempts to identify predictors of outcome often included patients suffering from schizophrenia and neurotic conditions as well as patients suffering depressive illness. Many of the correlates of recovery were simply characteristics of depressed patients as opposed to schizophrenic or neurotic patients.

No studies have included a comparison group of patients who receive no treatment at all, and only a few studies have considered patients who received some other physical treatment such as antidepressant drugs. Thus, we do not know if putative predictors are markers of a specific response to ECT alone rather than markers of the likelihood of spontaneous recovery or a good response to any physical treatment for depressive illness. Indeed, Hobson (1953) noted the similarity between the clinical features he associated with recovery after ECT and those already noted to be associated with a favourable outcome of depressive illness before ECT was available. This methodological problem is more significant today now that drug treatments for depressive illness are more widely available and many patients treated by ECT have already failed to respond to antidepressant drugs.

There are important theoretical and practical difficulties in the measurement of clinical outcome. There is no agreed definition of recovery after ECT. There is debate about the quantitative improvement that is required, and about the timing of this assessment. When follow-up is extended beyond the period of hospital stay, the method of assessment may be unsatisfactory; for example, some recent outcome studies have relied on follow-up by telephone. The majority of patients with endogenous depressive illness do well in the short term after ECT, but there is a greater variability of outcome as the length of follow-up is extended. Recent outcome studies have found that less than one-third of patients remain well six months after ECT (Coryell & Zimmerman, 1983; Lipman et al, 1986b; Katona et al, 1987). This review will concentrate on contemporary studies which use operationally defined depressed patients and clear outcome measures.

EEG studies
There is a higher prevalence of abnormal activity on the EEG among patients receiving ECT than in the general population (Mosovich & Katzenelbogen, 1948; Kennard & Willner, 1948). These abnormalities are more likely in older patients but show no relationship to clinical diagnosis. Some studies have found that patients with a normal (alpha) EEG record have a better outcome than patients with abnormal tracings, but this has not always been replicated.

Shagass (1954) estimated 'emotional arousal' by giving sodium amytal intravenously until the EEG showed an increase in beta activity, and this point was defined as the sedation threshold. Patients with low thresholds were usually suffering from psychotic depression and had a good prognosis with ECT. The inter-rater reliability of the test was low (Thorpe, 1962), and its usefulness as a predictor was not confirmed (Roberts, 1959).
During a course of ECT, the interictal EEG shows progressive reduction of the mean frequency and an increase in the mean amplitude. The degree of slowing is related to the number and frequency of seizures and, to a lesser degree, the types of current and placement of electrodes (Small et al, 1978; Fink, 1979). There is, however, great variability among patients in the amount, rate and persistence of EEG slowing after ECT, which only becomes prevalent after the third treatment. Roth et al (1957) were able to detect EEG slowing at an earlier stage of treatment after the injection of a standard amount of sodium thiopentone within 3–4 hours after a fit; however, they concluded that thiopentone-induced delta activity had only a small bearing on the immediate outcome of ECT.

**Autonomic reactivity**

The Funkenstein test (Funkenstein et al, 1948) measured the changes in blood pressure to injected adrenaline and methacholine. Patients in whom a chill developed after methacholine and patients in whom blood pressure rose more than 50 mmHg after adrenaline and fell and remained low after methacholine improved after ECT. Although reviewers suggested the test merited further development (Rose, 1962; Thorpe, 1962), they also criticised it adversely because of its low reliability, its uncertain physiological significance and its failure to take account of the effects of age.

Prudic et al (1987) studied 34 depressed patients throughout a course of ECT and found no cumulative pattern in either heart rate or blood pressure after treatment. Cardiovascular changes were not related to treatment or outcome variables, and it seemed that only age and pretreatment heart rate were predictive of cardiovascular change.

**Monoamines and metabolites**

The original catecholamine hypothesis of depressive illness (Schildkraut, 1965) arose from the observations that drugs causing depletion of brain noradrenaline produced depression, and drugs that increased or potentiated brain noradrenaline alleviated depression. Contrary to the original hypothesis, depressed patients often have increased plasma catecholamine concentrations. It has been suggested that the increase in plasma catecholamine concentration is associated with a vulnerability to stress (Cooper et al, 1985) or anxiety (Wyatt et al, 1971) or melancholia (Roy et al, 1985). No relationships have been reported between baseline plasma catecholamine concentrations and clinical outcome after ECT.

The principal metabolite of central nervous system noradrenaline is believed to be 3-methoxy-4-hydroxy-phenylglyicol (MHPG), which may be measured in urine. There is no relationship between the clinical response after ECT and the urinary excretion of MHPG (Sharma et al, 1986) or the cerebrospinal fluid (CSF) concentrations of the metabolites of noradrenaline, dopamine or serotonin (Aberg-Wistedt et al, 1986).

Plasma adrenaline and noradrenaline concentrations rise after ECT (Weil-Malherbe, 1955; Havens et al, 1959). Heightened sympathetic activity is not essential to treatment outcome, as the injection of barbiturate suppresses this response without reducing therapeutic efficacy.

**Calcium**

The introduction of lithium resulted in the study of mineral metabolism during depression. Ottosson (1974) has argued that the changes in sodium, potassium and water metabolism are secondary to recovery from depression and are not a direct effect of ECT. Since disorders of calcium metabolism are associated with mood disorder, there has been particular interest in calcium metabolism during recovery from depressive illness. Successful treatment of depressive illness by either imipramine or ECT is associated with decreased urinary excretion of calcium (Flach, 1964), and a positive calcium balance (Fragalla & Flach, 1970). Carman et al (1977) found that calcium concentration falls in both the CSF and serum during a successful course of ECT, and reviewed mechanisms by which calcium might alter mood. ECT may alter the distribution of calcium in the brain (Barkai & Nelson, 1987). The dynamics of calcium metabolism during ECT merit further study, although these alterations are not specific to ECT and there is no evidence that serum calcium concentrations before ECT are useful predictors of outcome.

**Cortisol**

Increased activity of the hypothalamic–pituitary–adrenocortical (HPA) axis is common in depressive illness. Elevated cortisol concentrations have been reported in the plasma (Gibbons, 1964), urine (Carroll et al, 1976a) and CSF (Carroll et al, 1976b) of depressed patients. Raised plasma cortisol concentrations are found in other psychotic illnesses and are not specific for severe depressive illness (Christie et al, 1986). Serum cortisol concentration are weakly correlated with the severity of depression (Deakin et al, 1983; Whiteford et al, 1987), but
there is no relationship between serum cortisol concentration before ECT and recovery from depression after ECT (Deakin et al, 1983).

Endocrine challenge tests

Endocrine challenge tests are used in two ways in ECT research. First, patients who respond rapidly to ECT may have a common physiopathology identified by a specific pattern of endocrine dysfunction (Fink, 1979). The two most common endocrine challenge tests used to test this hypothesis are the dexamethasone suppression test (DST) and the thyrotrophin-releasing hormone (TRH) stimulation test. Secondly, neuroendocrine tests may be used to assess monoamine neurotransmitter function in depressed patients (Checkley, 1980). Such tests make use of the role of monoamines in the control of the release of anterior pituitary hormones. The availability of radioimmunoassays for growth hormone (GH) has enabled the control of the release of GH to be studied in detail.

Dexamethasone suppression test

A feature of the increased activity of the HPA axis common in depressive illness is a resistance to normal feedback inhibition on the release of cortisol. Indeed, Carroll et al (1981) recommended that resistance of the HPA axis to dexamethasone was a specific laboratory test for endogenous depressive illness. Early studies by this group had suggested that during successful treatment of depressive illness the DST results gradually approach normal values (Carroll et al, 1976c). Coryell (1982) found that patients treated by ECT who showed resistance of cortisol release to dexamethasone in the DST (i.e. DST non-suppressors) improved with ECT more than DST suppressors. Other small studies found that early normalisation on the DST (by the fourth to sixth treatment) was predictive of a good clinical response. Those patients in whom the DST results failed to normalise had a poor clinical outcome (Dysken et al, 1979; Greden et al, 1980; Albala et al, 1981; Papakostas et al, 1981).

Subsequent studies have challenged these early findings. In a study of nine patients, Decina et al (1983) showed that during and immediately after a course of ECT, cortisol levels after dexamethasone became elevated rather than depressed. The increase in cortisol release was independent of clinical response to ECT. Five further studies have investigated the value of the DST as a predictor of the short-term outcome after ECT in a total of 154 depressed patients (Katona & Aldridge, 1984; Lipman et al, 1986a; Modai et al, 1986; Devanand et al, 1987; Fink et al, 1987). All these studies used operationally defined groups of depressed patients and comparable definitions of DST non-suppression, and categorised patients by outcome. There was no evidence either individually or collectively that DST status immediately before ECT was predictive of short-term outcome after ECT. Four subsequent studies have investigated the relationship between DST status and clinical outcome six months after treatment with ECT in a total of 130 depressed patients (Coryell & Zimmerman, 1983; Lipman et al, 1986b; Fink et al, 1987; Katona et al, 1987). There was no difference in outcome between initial DST suppressors and non-suppressors. The first two studies found that persistent non-suppressors had a better clinical outcome than did the initial non-suppressors who normalised after ECT, but this finding was not confirmed by the later studies. A confounding factor, however, was that the timing of the final DST was not standard.

These results may seem disappointing in view of early enthusiasm about the value of the DST as a predictor of clinical response to antidepressant treatment. Recent reviews, however, have found that DST status adds little to the prediction of short-term antidepressant response (e.g. Arana et al, 1985). Coryell (1986) suggested that the effect of ECT on the diencephalon may invalidate the DST as a marker of clinical response. Lipman et al (1986b) supported the view of Abrams (1982), who felt that once depressed patients were selected for ECT, there was not enough variability in this sample from which to predict outcome. Certainly, patients selected for ECT are not typical of endogenously depressed patients; for example, they have a higher prevalence of DST non-suppression and a greater prevalence of psychosis, and many will have failed to respond to antidepressant drugs. Patients included in studies involving the DST are even more highly selected because patients with significant weight loss, physical illness, personality disorder, and substance abuse are excluded.

TRH stimulation test

In 1972, two groups reported that a proportion of depressed patients have a blunted thyroid-stimulating hormone (TSH) response to TRH (Prange et al, 1972; Kastin et al, 1972). These reports stimulated a search for treatment-associated changes in the TRH stimulation test during treatment. Most of this work concerned treatment with antidepressant drugs. However, Coppen et al (1980b) reported that there was a non-significant reduction in the TSH response
to TRH in five patients after ECT. They did not report any association between TSH release before ECT and outcome. Papakostas et al (1981) tested seven patients before and after ECT and found no relationship between the TRH test and clinical outcome; however, as the authors admitted, their sample was too small to draw any conclusions. In the largest study to date, of 23 patients with major depressive disorder, Decina et al (1987) confirmed that the peak TSH response to TRH was decreased after ECT. This effect was consistent across individuals and was not related to clinical outcome. There was no difference between the mean TSH response to TRH in the responders and non-responders before ECT. Unfortunately, data are not provided on individual patients, although the authors state that the test has no predictive value. Kirkegaard & Faber (1986) found that a blunted TSH response was associated with an increased serum concentration of free thyroxine.

The TRH stimulation test may be useful in research to detect physiological changes during a course of ECT. The usefulness of the test in identifying depressed patients who will recover with ECT has not been proven, but must be limited because only 25-30% of euthyroid depressed patients have a blunted TSH response to TRH (Albala et al, 1984).

Neuroendocrine tests of monoamine function

Drugs which stimulate specific monoamine systems and release GH from the anterior pituitary have been used to study the mode of action of ECT (Cowen, 1986). Although there is evidence from animal studies that repeated electroconvulsive shocks result in functional changes in brain monoamine pathways (Grahame-Smith et al, 1978), studies in depressed human beings have produced conflicting results. Neuroendocrine responses are complex and there are many steps between the administration of a drug and the measurement of a hormone response in plasma. Three drugs have been used in challenge tests in depressed patients receiving ECT. Clonidine (alpha-2 agonist), apomorphine (dopamine agonist), and amphetamine (non-specific monoamine agonist) stimulate the release of GH. Although Costain et al (1982) found a significant increase in the GH response to apomorphine after a course of ECT (thus supporting the hypothesis that ECT produces an enhancement of dopamine-mediated responses in the brain), this finding was not confirmed by Christie et al (1982). Costain et al (1982) noted that they had excluded from their study patients with a high basal concentration of GH, and when such patients were included in the analysis, the increase in apomorphine response following ECT was no longer significant. Slade & Checkley (1980) found no change in the release of GH by either clonidine or methylamphetamine in depressed patients after a course of ECT.

Plasma prolactin concentration is increased by the administration of TRH. Serotonin is the transmitter implicated in this stimulation of prolactin release. Coppen et al (1980a) found that prolactin release after TRH was increased after ECT; however, there was no association between prolactin release before ECT and clinical recovery. The release of prolactin may be inhibited by apomorphine, which is thought to be mediated by dopamine-containing neurons. Baldin et al (1982) found that a course of ECT enhanced the inhibition of the release of prolactin by apomorphine. There were no correlations between serum prolactin concentrations before or after apomorphine and clinical recovery after ECT.

The interpretation of such challenge tests is complex. For example, the release of GH is influenced by age, ovarian function, time of day, baseline concentration, alcohol, and concomitant psychotropic drug therapy (Checkley, 1980). Specific agonists or antagonists to monoamine receptors in the central nervous system may be of value in research, but with interpretation confounded by so many variables, they have no established role in clinical practice.

Seizure threshold

The traditional view of the goal of ECT is that it is to elicit a generalised tonic clonic seizure of adequate duration, delivering the minimum possible intensity of electrical current. This recommendation derives from research suggesting that the antidepressant effects of ECT are tied to seizure elicitation, whereas increasing the stimulus intensity produces unnecessary cognitive side-effects (e.g. Oottoson, 1960). Seizure threshold, defined as the minimum electrical stimulus necessary to elicit adequate generalised seizures, varies 12-fold among drug-free depressed patients (Sackeim et al, 1987a). The practical implication of this finding is that in fixed-stimulus ECT, patients with a low seizure threshold can receive electrical stimuli many times greater than that necessary to elicit a generalised seizure. This may increase the degree of cognitive side-effects substantially. Patients with a high seizure threshold will have shorter seizures than patients with a low threshold (Sackeim et al, 1987b). This led Sackeim and colleagues to investigate the relationship between seizure threshold at the start of a course of ECT and...
clinical outcome. Non-responders to bilateral ECT had a mean seizure threshold almost twice that of responders. There was no difference in seizure threshold between responders and non-responders to titrated right unilateral ECT (Sackeim et al., 1987b). The efficacy of titrated ECT (i.e. the use of the minimum electrical stimulus to elicit a generalised seizure) has not been assessed; but the effects of seizure threshold on outcome and cognitive side-effects clearly merit further study.

Measures of seizure activity
There is a "general belief that convulsive activity in the brain is the crucial ingredient" of ECT (Kendell, 1981). The seminal work of Ottosson (1960, 1962) is often cited as evidence. Ottosson demonstrated that seizures shortened by the administration of lidocaine were less efficient in relieving depressive illness than self-limited grand mal seizures. It is less commonly repeated that Ottosson (1962) found that the duration of the grand mal seizure had no significant relationship to therapeutic efficiency:

"It seems, therefore, to be of no importance whether a person develops long or short grand mal seizures, the essential thing being that they are grand mal self-limited seizures."

There may be a range of electrophysiological response to ECT, from the so-called 'missed seizure' where there is a failure to induce any epileptic activity; through types of minor seizure similar to petit mal; to classical tonic clonic generalised activity (Small et al., 1978). There is rough agreement about what constitutes an adequate tonic clonic seizure. The proposed definitions vary with the method used to monitor seizure activity, namely, 30 seconds of generalised muscle activity (d'Elia et al., 1983), 25 seconds of muscle activity in a forearm isolated from the muscle relaxant by a tourniquet (Fink, 1979), or 30 seconds of epileptic activity on EEG (Fink, 1979). The American Psychiatric Association (1978) recommended that "a seizure lasting less than 25 seconds may not be adequate"; observation alone, the tourniquet method, and EEG monitoring were all practical methods to ensure that seizures were adequate.

There is only circumstantial support for these definitions. For example, several authorities cite the work of Small et al. (1978) as support for a minimum seizure duration of 25 seconds. In fact, these authors did not define an adequate seizure but noted that minor seizures tended to last less than 25 seconds, and were not followed by electrical silence or a phase of delta wave activity on EEG. There is now evidence that there is no relationship between individual seizure length (measured by observation or EEG) and clinical change during a course of ECT (Weiner et al., 1983; Rich & Black, 1985; Zorumski et al., 1986). It may not be feasible to define a minimum length for a therapeutic seizure, as time alone takes no account of the degree of spread of seizure activity over the cortex or throughout the brain. This is a debate which merits further research.

Generalised tonic clonic seizures are an essential component of ECT and thus it is important to ensure that such a seizure occurs at each ECT treatment. The induction of satisfactory cerebral seizures does not, however, guarantee that a course of ECT will be successful. There is no correlation between individual seizure length and clinical outcome and thus seizure length cannot be used to predict recovery.

Release of anterior pituitary hormones
The effects of ECT on temperature control, appetite, weight and autonomic activity have long implicated the hypothalamus in the physiology of ECT (Fink, 1979). A convenient means to study at least some aspects of hypothalamic activity is by the measurement of the release of anterior pituitary hormones which are released under the control of the hypothalamus. The popularity of this approach increased with the knowledge that neurotransmitters implicated in the pathophysiology of depressive illness (serotonin, noradrenaline and acetylcholine) were also involved in the regulation of the hypothalamic–pituitary system. Thus the precise extent and timing of anterior pituitary hormone release after ECT may also provide information about the effects of ECT on neurotransmitter function.

The most consistently reported endocrine effect of ECT is a rapid increase in plasma prolactin concentrations, reaching a peak 10–15 minutes after treatment. However, simulated ECT also increases plasma prolactin concentration twofold (Deakin et al., 1983), which suggests that prolactin release may occur as a response to the stress of the ECT procedure. Balldin (1982) reported that the increase in plasma prolactin concentration after ECT correlated with the length of seizures estimated by clinical observation, but this has not been confirmed (Aperia et al., 1985; Scott et al., 1986). The extent of the increase in plasma prolactin concentration at the time of the first treatment was unrelated to the extent of clinical recovery after ECT in two studies (Deakin et al., 1983; Scott et al., 1986). However, Abrams & Swartz (1985) reported that in 16 male
melancholics, free of drugs which might affect plasma prolactin concentration, there was a correlation between a large prolactin response to ECT and a slow treatment response.

Plasma concentrations of adrenocorticotrophin and luteinising hormone also rise after ECT, but the extent of these increases is not related to clinical improvement (Whalley et al., 1987). The effects of ECT on plasma concentrations of growth hormone and TSH have been disputed. There is great variability in the effects of ECT on the release of growth hormone in different patients, but the effect of the first ECT on growth hormone release is not related to the extent of recovery (Scott et al., 1986). Dykes et al. (1987) have clarified the effect of ECT on the release of TSH. The release of TSH after ECT was closely correlated with the extent of seizure activity measured by EEG, and only occurred consistently when seizures lasted at least 30 seconds.

Several groups have suggested that endogenous opioids may be involved in the mode of action of ECT. A research strategy to assess the activity of endogenous opioids is to measure plasma concentrations of beta-endorphin which is released from the anterior pituitary. ECT produces a transient increase in plasma immunoreactive beta-endorphin concentrations (Alexopoulos et al., 1983; Misiaszek et al., 1984), although the time course of this increase has not been well described. In a study of nine depressed patients, Weizman et al. (1987) found that the effect of the sixth ECT on plasma beta-endorphine concentrations was twice that of the first ECT. There are no reports of any correlation between the extent of the release of beta-endorphin and clinical recovery.

In summary, the neuroendocrine effects of ECT may be a correlate of stress, seizure activity or the antidepressant effect of ECT. The release of anterior pituitary hormones after ECT has not consistently correlated with the antidepressant effects of ECT, and is unlikely to be useful in the prediction of clinical outcome. The use of EEG-monitored ECT may provide further information about which of these endocrine responses are correlated with seizure activity itself.

**Release of posterior pituitary hormones**

The posterior pituitary (or neurohypophysis) releases two peptide hormones, arginine vasopressin and oxytocin, which are both synthesised in association with a neurophysin peptide which is released mole for mole with its hormone. Measurement of plasma neurophysin concentrations therefore provides an accurate guide to hormone release, with the advantages of easier detection and longer half-life. Whalley et al. (1987) found that ECT stimulated an increase in plasma concentrations of both the vasopressin-associated neurophysin (hNpI) and the oxytocin-associated neurophysin (hNpII). This hormonal pattern was not found in a comparison group of surgical patients undergoing cholecystectomy. This small study suggested that the rise in plasma hNpII concentration after the first application of ECT was correlated with the extent of recovery from depressive illness. This correlation was confirmed in a subsequent study of 25 depressed patients (Scott et al., 1986). The peak hNpII response to ECT in the group with a good outcome at two months was three times that in the poor outcome group. One explanation of this finding would be that the release of hNpII is a sensitive correlate of seizure activity in the midbrain, and that greater seizure activity there is associated with a better response to ECT. A further study has confirmed that the hNpII response to the first ECT is correlated with outcome (Scott et al., in preparation), but has found no association between the release of hNpII and seizure activity measured by EEG. The extent of the rise in hNpI was not related to clinical outcome at two months. The association between hNpII release and clinical improvement is unexplained, but the predictive value of this test merits further study. Unfortunately, the assay of neurophysins is a specialised technique which is unlikely to become widely available.

**Conclusions**

The majority of contemporary depressed patients selected to receive ECT will do well in the short term, but a small yet significant minority will gain little or no benefit from this controversial treatment. Careful assessment and diagnosis of endogenous-type depressive illness remains the single most important step in the selection of depressed patients for ECT. Once depressed patients are selected to receive ECT, the diagnosis of endogenous depressive illness does not guarantee recovery (Coryell & Zimmerman, 1984). Weight loss, early morning waking and somatic delusions may be the clinical features of endogenous depressive illness which best predict a good outcome after ECT (Carney et al., 1965). There are, however, major methodological limitations to such clinical prediction studies. Indeed, Crow et al. (1984) have argued that the only consistent clinical predictor of a specific response to ECT is the presence of delusions. It has been argued that the use of clinical features alone will not improve the ability to predict outcome after ECT. Consequently,
there have been many attempts to identify biological measures which may select depressed patients who will respond well to ECT.

There have been few recent studies which have compared clinical and biological measures in the selection of patients for ECT. Katona et al (1987) found that the Newcastle ECT Predictor Scale (Carney et al., 1965) was useful in predicting both immediate and six-month outcome, but DST status was unsuccessful in predicting either outcome in 26 depressed patients. There are no physiological measures or tests which are superior to clinical criteria in the selection of depressed patients for whom ECT would be an effective treatment.

Depressed patients have a wide range of physiological responses to ECT. Exposure to ECT itself may provide a better guide to prognosis, in much the same way that a dynamic hormone challenge test is more informative than the estimation of a random hormone concentration. The most important physiological interaction between the patient and the ECT stimulus is that a self-limited tonic clonic seizure occurs, and this must be confirmed by the attendant psychiatrist. The present recommendation that the seizure must last at least 25 seconds is an arbitrary one. Further study is necessary to clarify the minimum requirements for a successful seizure. The relationship of initial seizure threshold to clinical response and cognitive side-effects merits further study.

Although a generalised tonic clonic seizure is an essential component of successful ECT, this is not always sufficient. Endogenously depressed patients can experience satisfactory seizures and yet fail to recover with ECT. The only physiological measure at the first use of ECT which has been shown to correlate with recovery is the release of hNpII (the oxytocin-associated neurophysin). It is not known if this putative predictor is a marker of a specific response to ECT alone rather than a marker of impending spontaneous recovery or a good response to any physical treatment for depression. Unfortunately, at present the estimation of hNpII concentrations requires a sophisticated assay which is not available for widespread clinical use. The nature of the association between the release of hNpII and recovery after ECT is unknown and merits further study. There is a need for studies which compare the predictive power of clinical and physiological measures in contemporary depressed patients selected for ECT.

Acknowledgements

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Coppen, A., 16

SCOTT


Reliability of the Application of a Kinetic Model of Hormone Release: Prolactin and Oestrogen-Stimulated Neurophysin After Electroconvulsive Therapy


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Summary: Pituitary hormone release after electroconvulsive therapy (ECT) may provide important information about certain of the effects of ECT on neurotransmitter function. Previously we quantified pituitary hormone release by the increase in the area under the hormone concentration/time curve. Swartz has rightly pointed out that this method ignores the rate of elimination of hormone and cannot be a measure of total hormone released. Swartz has proposed a kinetic model of hormone release, and in this paper we assess the reliability of parameters derived from it when applied to our own data on the effects of ECT on the release of prolactin and oestrogen-stimulated neurophysin. The deviations between observed and predicted values were small when only five post-ECT samples were used. Contrary to expectations, the goodness of fit did not improve when the number of sampling points was increased to nine after ECT. It was possible to fit a unique curve to the observed data in only 28 of 54 data sets. The reasons for these findings are discussed.

Key Words: Electroconvulsive therapy—Prolactin—Oestrogen-stimulated neurophysin—Pharmacokinetics.

Editor's comment: The Letter to the Editor by Swartz, pp 185–189 in this issue, is a response to this article.

Our previous work has shown that there are rapid and substantial increases in the release of prolactin and the neurophysins from the pituitary after electroconvulsive therapy (ECT) (Scott et al., 1986; Whalley et al., 1982; Whalley et al., 1987). We found that the extent of the increase in the release of oestrogen-stimulated neurophysin (ESN), but not prolactin, correlated with the extent of

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improvement in depressive illness on completion of treatment. In these studies we quantified the increase in pituitary hormones by the increase in the area under the hormone concentration/time curve. Swartz (1985a) has rightly pointed out that since this method ignores the rate of elimination of hormone from the blood, it cannot be a measure of the total amount of hormone released from the pituitary. It does, however, measure the availability over time of the released hormone.

Swartz (1985a) tested a more accurate model of hormone release and elimination using data collected in his study of prolactin release by ECT. The model can be written as the kinetic equation

\[ C = P[e^{-E(T-L)} - e^{-R(T-L)}] \]

where \( T \) is the time since the end of the seizure, \( C \) is the elevation of prolactin concentration over baseline, \( P \) is the total prolactin release, \( E \) is the fractional elimination rate, \( R \) is the fractional release rate, and \( L \) is the latency. The assumptions implicit in this model were described in a previous paper (Swartz, 1985b). Swartz estimated the coefficients of release for individual treatments and described an average time course of the release of prolactin after ECT. Recently, Swartz and Quock (1987) argued that the routine application of this model would improve the accuracy and understanding of studies of pituitary hormone release.

This work prompted us to re-examine our earlier data to assess the reliability of this kinetic model in describing the release of prolactin and ESN (Scott et al., 1986). In this study, plasma hormone concentrations were estimated at 10 time points after ECT (+2.5 to +240 min), whereas Swartz used hormone concentration at only 6 time points (+5 to +60 min). Not only does our study give a more accurate description of the time course of hormone concentration after ECT, but it will be a more stringent test of the ability of this kinetic model to describe the observed data.

**METHODS**

**Curve Fitting**

When attempting to fit a curve to observed data, the minimum number of data points is equal to the number of unknown parameters in the equation. If there are errors associated with the measurements, additional points are required to give confidence in the values of the parameters. Swartz’s model assumes a smooth curve for the sake of simplicity.

The data Swartz (1985a) used to estimate these unknowns were based on six sample points after ECT. However, Swartz eliminated points that deviated significantly from a smooth curve. The data set consisted of 16 ECT treatments, but in only five of these treatments were all six sampling points used. The majority of the data sets had only five sample points because of eliminated or missing data. We hoped to improve the accuracy of the estimates of the unknowns by using data from nine sampling points. We also were able to assess reliability by forming two subsets of data of five sampling points each in which only the baseline value and the final (+120 min) value were the same.
patients

The data used to assess the reliability of the kinetic model was taken from our previous study (Scott et al., 1986). The sample consisted of the first nine patients—five women (mean age 47 years) and four men (mean age 51 years). The study was restricted to the first nine patients only because of the considerable time taken to analyse each data set. All patients fulfilled the Research Diagnostic Criteria (RDC) (Spitzer et al., 1976) for major depressive disorder, and five of these patients had either delusions or hallucinations. Only one patient was free of psychotropic drugs. Five patients received an antidepressant drug alone, two patients received a neuroleptic drug alone, and one patient received amyllobarbital.

ECT

ECT was given between 9 and 10 a.m. after an overnight fast. No routine premedication was given. Anaesthesia was always induced by thiopentone and suxamethonium. A standard electrical stimulus was given (600 mA over 5 s in 2 msec pulses at 100 Hz), and the cuff method was used to ensure that a cerebral seizure occurred. Seven patients received unilateral ECT (D’Elia placement) and two patients bilateral ECT (bitemporal placement).

Hormone Measurements

Plasma prolactin and ESN concentrations were measured at the first treatment of a course. Blood samples were withdrawn at 13 sampling points (-60, -30, -1, +2.5, +5, +7.5, +10, +12.5, +15, +30, +60, +120, and +240 min). Plasma was separated by centrifugation after collection of the last sample and stored at -40°C. Plasma hormone concentrations of prolactin and ESN were determined by radioimmunoassay kits from the National Institute of Arthritis, Diabetes, and Diseases of the Kidney. All samples were assayed in duplicate, and results are the mean of these two values. The sensitivities of the assays (90% B/Bo) were 2 ng/ml for prolactin (50 µl sample) and 1 ng/ml for ESN (100 µl sample). The mean coefficients of variation between and within assays of two or three quality controls for each assay were below 10%. For each hormone, the plasma concentrations reported in this paper were measured in the same assay.

Statistical Procedure

The data were simplified by averaging the three pretreatment values to give a more reliable baseline measure and excluding the 240 min sampling point because it was the furthest point from ECT and may have been subject to confounding influences such as the intake of psychotropic drugs at lunch time. We used three sets of sampling points for each individual—set C of the full data set of nine sampling points at 2.5, 5, 7.5, 10, 12.5, 15, 30, 60, and 120 min after ECT; set A of the five sampling points at 5, 10, 15, 60, and 120 min; and set B also of five sampling points but at 2.5, 7.5, 12.5, 30, and 120 min. The three sets of data for
each patient were run separately for prolactin and ESN, using the BMDP PAR program as Swartz suggested.

The process of curve fitting is done iteratively and is analogous to trying to find the lowest post in a terrain by choosing a starting place and then travelling a certain distance either north or south according to which direction is downhill and repeating that for the east-west direction and then back to north-south until you cannot find a move that is downhill. This you assume is the lowest point in the terrain. It need not be so if the terrain is very uneven and you are stuck in a local depression, but not necessarily the lowest point of all. This yields a nonunique result. A different problem arises when the starting point is rather flat ground, and there is no obvious downhill in any direction. This yields a nonconverging solution. In 11 of his 16 results, Swartz ran afoul of one or other of these problems, nor were we immune to them. The BMDP PAR program is also rather slow and often requires several runs at the data using different starting points to check for the above. For this reason we only looked at the first 9 subjects rather than all 25 of them. For each hormone, all the samples were measured in the same assay.

The reliability of the estimates of the four parameters in the kinetic model was assessed in three ways. The split-half reliability (values from sample A versus values from sample B) and the correlations between the full data set C with each of the subsets A and B were measured using Pearson’s Product-Moment Correlation.

RESULTS

The three pretreatment values were averaged to give a more reliable baseline measure for each hormone. The increase in plasma concentrations of prolactin (Fig. 1) and ESN (Fig. 2) are shown. Table 1 gives the average plasma concentrations of each hormone at individual sample points.

Each of the nine treatments yielded one full data set for prolactin release and one full data set for ESN release. Each of the full data sets was used in three ways to estimate the four parameters in the kinetic equation. Thus there were 54 attempts at curve fitting. In only one-half of these attempts (28 of 54) was it possible to obtain a unique and converging solution.

Two patients had received neuroleptic drugs that are known to alter the release of prolactin (Ohman and Axelsson, 1980). In addition, there was one patient in whom the release of prolactin had two separate peaks 10 min apart (Fig. 1). When data sets from these three patients were set aside, it was still only possible to obtain a unique and converging solution in one-half of the remaining data sets (20 of 36). Thus the inability to obtain unique and converging solutions for the kinetic equation could not be explained by the presence of the data from these three patients, and they were included in all further analyses.

The three measures of reliability for each parameter in the prolactin and ESN data sets are given in Table 2.

An example of a comparison of estimates is given in Table 3, which lists the observed and predicted values of plasma prolactin concentration for the three data sets in one patient in whom it was possible to obtain a unique and converging
solution to the kinetic equation. The differences between observed and predicted values are less when only five sampling points are used, compared with the full nine sampling points. This was a consistent finding. The absolute differences between observed and predicted values are small, and the estimates of total hormone release differed by 40% over three analyses of similar curves. When it was not possible to find a unique and converging solution for the equation, the estimates of total hormone release differed by more than a factor of four from three analyses. This could be so even when the solutions to the equation produced absolute differences between the observed and predicted concentrations of the same magnitude as the example in Table 3.

**DISCUSSION**

The split-half reliability of \( P \) (total hormone release) is high at 0.89 for both prolactin and ESN. On the other hand, the correlations of each half with the full data set are 0.29 and 0.43 in the case of prolactin, which is low, and 0.63 and 0.88 for ESN, which is acceptable. One would normally expect that the correlation of each half with the whole would be, if anything, rather better than the correlations between the two halves because of the inclusion of some identical points in the two sets.

The split-half reliability for \( L \) (latency between ECT and release) is acceptable in the case of prolactin at 0.67 but is only 0.50 in the case of ESN. The estimates of \( R \) (release rate) are reliable for prolactin, but reliability is poor in the case of
FIG. 2. Increase in plasma ESN concentrations after the first treatment of a course of ECT in nine depressed patients. The pretreatment value is the mean of three samples.

ESN. The estimates of $E$ (elimination rate) are highly reliable in the case of ESN but unreliable for prolactin.

Further information was gained by direct comparison of estimates made. In general, the differences between observed and predicted data points were greater when the full data set of nine sampling points was used (an example from one

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Prolactin (ng/ml)</th>
<th>ESN (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$-1^a$</td>
<td>$16.4 \pm 7.3$</td>
<td>$1.6 \pm 0.2$</td>
</tr>
<tr>
<td>2.5</td>
<td>$18.9 \pm 7.0$</td>
<td>$2.5 \pm 0.2$</td>
</tr>
<tr>
<td>5.0</td>
<td>$31.4 \pm 9.7$</td>
<td>$2.5 \pm 0.2$</td>
</tr>
<tr>
<td>7.5</td>
<td>$34.3 \pm 9.6$</td>
<td>$2.5 \pm 0.1$</td>
</tr>
<tr>
<td>10.0</td>
<td>$37.6 \pm 10.1$</td>
<td>$2.4 \pm 0.2$</td>
</tr>
<tr>
<td>12.5</td>
<td>$38.9 \pm 10.6$</td>
<td>$2.3 \pm 0.2$</td>
</tr>
<tr>
<td>15.0</td>
<td>$39.3 \pm 10.3$</td>
<td>$2.2 \pm 0.2$</td>
</tr>
<tr>
<td>30.0</td>
<td>$35.2 \pm 9.7$</td>
<td>$2.1 \pm 0.2$</td>
</tr>
<tr>
<td>60.0</td>
<td>$24.6 \pm 8.3$</td>
<td>$1.7 \pm 0.2$</td>
</tr>
<tr>
<td>120.0</td>
<td>$16.9 \pm 7.6$</td>
<td>$1.6 \pm 0.2$</td>
</tr>
</tbody>
</table>

$a$ Mean of three pretreatment values.
TABLE 2. Three measures of reliability$^a$ of kinetic coefficients of hormone release after ECT for sets A, B, and C

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total amount of hormone released ($P$)</td>
<td>0.89</td>
<td>0.29</td>
<td>0.43</td>
<td>0.89</td>
<td>0.63</td>
<td>0.88</td>
</tr>
<tr>
<td>p value</td>
<td>$d$</td>
<td>NS</td>
<td>NS</td>
<td>$d$</td>
<td>NS</td>
<td>$e$</td>
</tr>
<tr>
<td>Latency ($L$)</td>
<td>0.67</td>
<td>0.76</td>
<td>0.50</td>
<td>0.50</td>
<td>-0.30</td>
<td>-0.20</td>
</tr>
<tr>
<td>p value</td>
<td>$b$</td>
<td>$b$</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Release rate ($R$)</td>
<td>0.69</td>
<td>0.79</td>
<td>0.94</td>
<td>-0.09</td>
<td>0.65</td>
<td>-0.01</td>
</tr>
<tr>
<td>p value</td>
<td>$b$</td>
<td>$b$</td>
<td>$d$</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Elimination rate ($E$)</td>
<td>0.10</td>
<td>0.17</td>
<td>0.75</td>
<td>0.92</td>
<td>0.90</td>
<td>0.98</td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>NS</td>
<td>$b$</td>
<td>$d$</td>
<td>$d$</td>
<td>$d$</td>
</tr>
</tbody>
</table>

$^a$ Pearson's product-moment correlations between estimates of coefficients derived from full data set C (nine sampling points) and two subsets A and B (five sampling points each). NS, not statistically significant.

$^b$ p < 0.05.

$^c$ p < 0.01.

$^d$ p < 0.001.

patient is given in Table 3. In addition, it was possible to find a unique and converging solution for the equation in only 9 of the 18 full data sets.

The kinetic model for the estimation of hormone release after ECT correctly takes account of the rate of elimination of hormone. Why then was the reliability of the parameters derived from this method so disappointing? One of the assump-

### Table 3. Goodness of fit shown for the three data sets for prolactin release in one patient free of neuroleptic drugs

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Actual</th>
<th>Predicted by data set:</th>
<th>Residuals (difference)</th>
<th>Curve fitting parameters for the data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>2.5</td>
<td>91</td>
<td>92</td>
<td>91</td>
<td></td>
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<tr>
<td>5</td>
<td>196</td>
<td>205</td>
<td>282</td>
<td>196</td>
</tr>
<tr>
<td>7.5</td>
<td>282</td>
<td>273</td>
<td>282</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>316</td>
<td>311</td>
<td>342</td>
<td></td>
</tr>
<tr>
<td>12.5</td>
<td>343</td>
<td>329</td>
<td>342</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>306</td>
<td>334</td>
<td>308</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>286</td>
<td>275</td>
<td>286</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>143</td>
<td>146</td>
<td>137</td>
<td></td>
</tr>
<tr>
<td>120</td>
<td>38</td>
<td>40</td>
<td>38</td>
<td>46</td>
</tr>
<tr>
<td>Mean</td>
<td>deviation</td>
<td>9.1</td>
<td>0.2</td>
<td>3.4</td>
</tr>
</tbody>
</table>

$^a$ Rise above mean baseline.
tions of the model is that the major determinant of hormone release after ECT is the seizure (Swartz, 1985b). As Swartz (1985a) has acknowledged, this may not be a valid assumption in the case of prolactin release after ECT, as the stress of anaesthesia and the procedure may also release prolactin. Deakin et al. (1983) have confirmed that simulated ECT can lead to a doubling in plasma prolactin concentrations. In his earlier analyses, Swartz excluded data sets that were inconsistent with a single stimulus to release, for example, when there were two peaks in release. We included all data sets.

Swartz (1985a) recommended that two samples are required before the peak to estimate latency and rate of release accurately. This sampling requirement was satisfied in the case of prolactin but not in the case of ESN. The peak plasma ESN concentration was usually observed at 2.5 min, which was the first sampling point after ECT. This probably explains the poor reliability of estimates of latency and release rate for ESN (Table 2). Peak neurophysin concentrations after ECT may occur within 1 min (Whalley et al., 1982), and the requirement for two blood samples to be withdrawn before this peak presents practical difficulties.

There may be other sources of sampling error. First, serum prolactin concentrations show considerable random fluctuations over the short term (McNeilly and Chard, 1974), and such fluctuations may reflect the neural mechanisms important in the control of their release (Willoughby et al., 1977). Second, blood samples are withdrawn from a peripheral vein far removed from the site of release of these hormones. There are marked changes in blood pressure and pulse after ECT, and the time lag between hormone release and arrival in the peripheral vein will vary in the first few minutes after ECT. Ideally, the time to withdraw each blood sample is constant, but there may be practical difficulties in withdrawing a blood sample smoothly from an uncoordinated post-ECT patient.

Our full data set consisted of nine sampling points after ECT. If this kinetic model of hormone release is valid, then we would suggest that even more frequent sampling is advisable. This would allow the calculation of a moving average to produce a smoother curve, which may lead to more reliable estimates of the coefficients. However, it is still not established that total hormone release is more relevant than availability (area under the hormone concentration/time curve) or maximum availability (peak), in predicting any differences in therapeutic response to ECT. Hopefully, ECT researchers will consider all three measures in the future.

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REFERENCES


